

An aerial photograph of a coastal city, likely Gold Coast, Queensland, Australia. The image shows a wide sandy beach in the foreground, with waves breaking onto the shore. In the background, a dense urban skyline is visible, featuring several prominent skyscrapers, including one with a distinctive geometric, crystalline facade. The sky is clear and blue.

**GOLD COAST
INTERACTIVE**

Biomarker Bonanza: Pioneering Precision in Macular Disease Diagnosis and Management

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PhD, BOptom(Hons), GradCertOcTher, FAAO, AFHEA



An invitation to learn



Referral roulette

Precision optometry

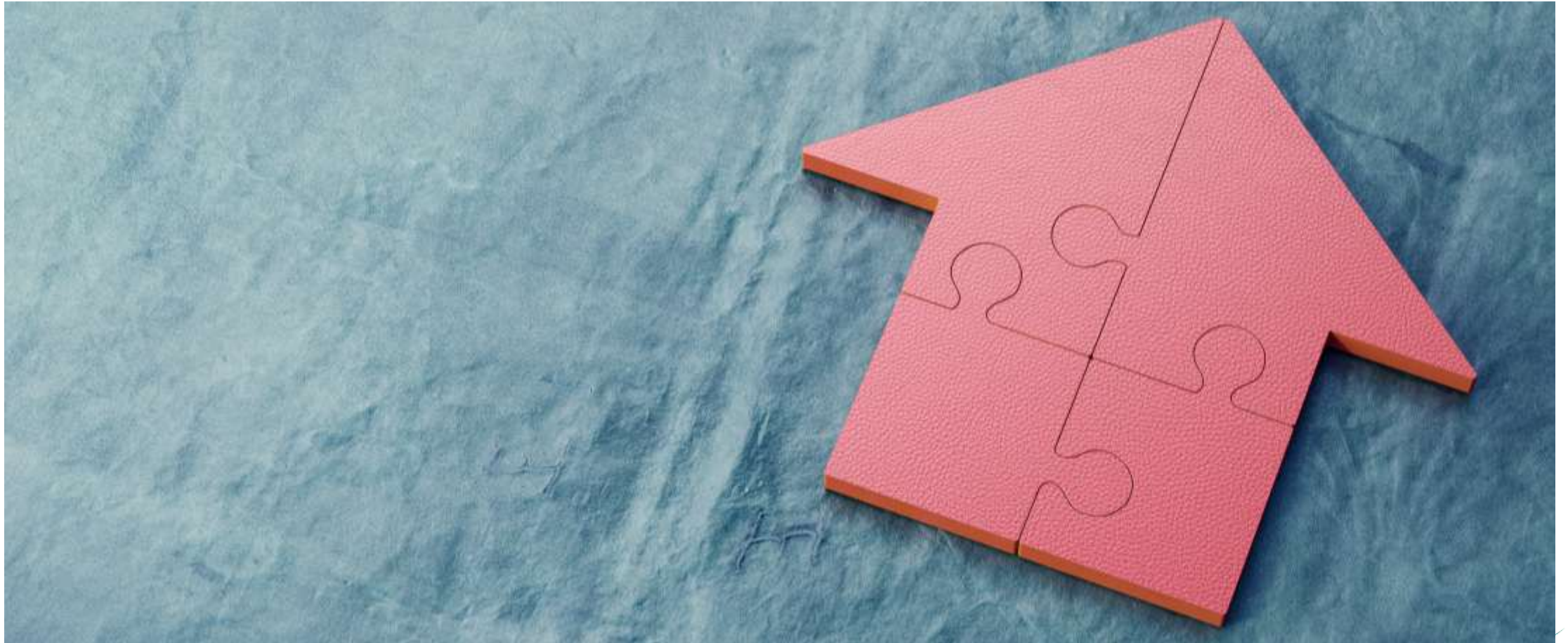


Which best describes the way you would like to practice if you were to encounter a patient with macular disease tomorrow?



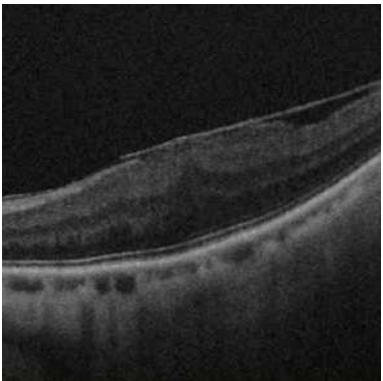
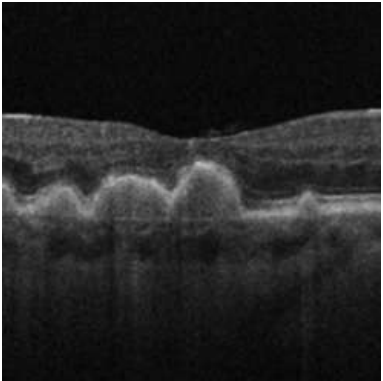
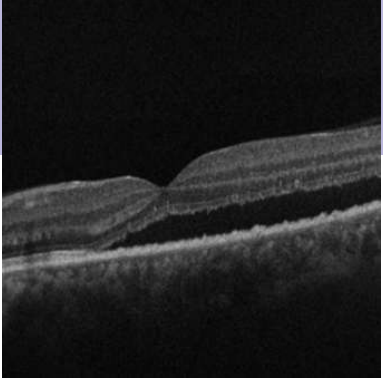
What stops you from practising in a more precise way?

An invitation to learn



Learning objectives

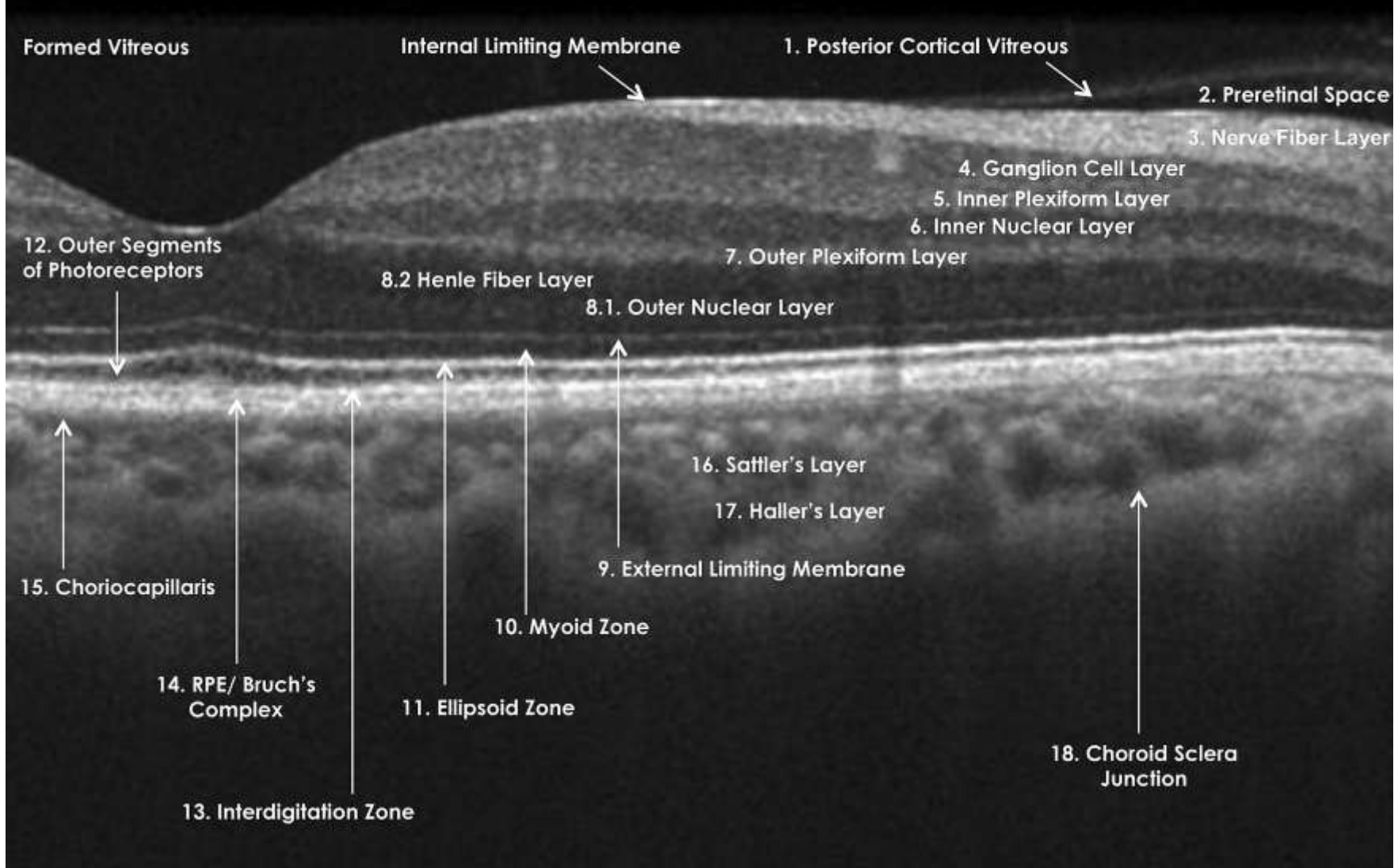
- By the end of this presentation, attendees should be able to:
 - Identify key retinal biomarkers associated with macular conditions
 - Infer the clinical implications of these biomarkers, and
 - Apply this knowledge to improve the diagnosis and management of macular disease



Outline

- Introduction to retinal biomarkers
- ‘Name that biomarker’ game (45mins)
- Group ‘trivia’
 - Three case studies
 - Diagnostic biomarkers in CSCR
 - Prognostic biomarkers in AMD
 - Predictive biomarkers in epiretinal membrane

International Nomenclature for OCT Meeting Consensus Normal OCT Terminology



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Assumed knowledge

What is a biomarker?

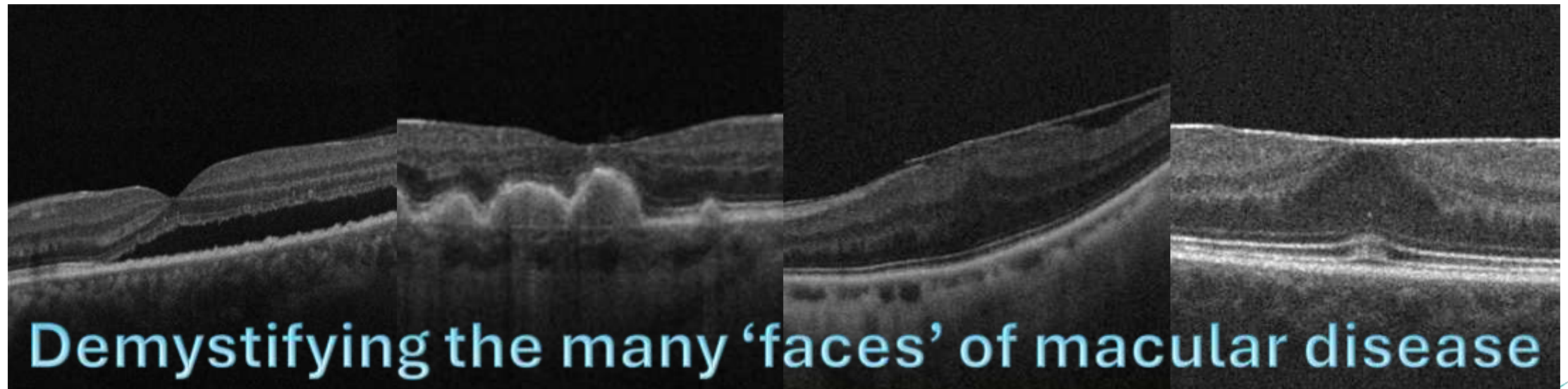
- Objectively measurable
- Indicator of normal biology, pathogenesis or therapeutic response



AI generated using MS Co-pilot

What is a biomarker? 'Practical' applications

- Useful to identify 'low' vs 'high'-risk
- To reduce the burden of care and improve outcomes
- Ocular biomarkers are intrinsically related to imaging



Puntmann VO. Postgrad Med J. 2009 Oct;85(1008):538-45.

Califf RM. Biomarker definitions and their applications. Exp Biol Med (Maywood). 2018 Feb;243(3):213-221

What is a biomarker? 'Practical' applications

- **Susceptibility:** identifying the risk of developing a disease in healthy adults
- **Screening:** screening for subclinical disease e.g., in family screening
- **Diagnostic:** recognising overt disease
- **Staging:** categorising disease severity to aid staging of impairment
- **Prognostic:** identifying likelihood of disease progression in patients with disease to aid monitoring
- **Predictive:** predict response to treatment or therapy

Name that biomarker (45 mins)

In your tables of 8, play a game based on celebrities/monikers where you each take turns giving clues to get your teammates to name that biomarker



Name that biomarker: Getting started



- The game takes about 5 minutes to learn.
- Divide your group into 2 teams.
- Deal 10 cards to each person. Everyone secretly chooses 5 that they like.
- Shuffle all the cards people chose into one deck, which will be used by both teams for the game. Put the other cards aside.
- The person who last saw a case of macular disease is team captain and goes first.

Name that biomarker: How to play

- The game is played in 3 rounds.
- In each round, the active player has 60 seconds to get their team to guess as many biomarkers as possible from the deck by giving clues about the biomarker description or clinical implications.
- **Learning objective: Identify key retinal biomarkers associated with macular conditions**



Name that biomarker: How to play



Round 1. Clue givers can say anything, except for the name itself



Round 2. Clue givers can say only one word



Round 3. Clue givers can only draw

- Teams keep the cards they guessed correctly to score after each round.
- Reshuffle skipped cards into the deck after each turn.
- Teams take turns giving clues. Each player should take a turn giving clues before teammates repeat. Go in clockwise order.
- Tips:
 - There is **no limit** to the number of guesses.
 - **Skipping is allowed** and highly encouraged!
- By the end, you will have been introduced to 24 different biomarkers!

Name that biomarker: cheat-sheet

CSCR

- Flat irregular pigment epithelial detachment
- Pachyvessels
- Choroidal thickness
- Retinal 'dipping'
- Inner choroid attenuation
- Cystoid macular degeneration

AMD

- ELM abnormality
- EZ abnormality
- IZ abnormality
- Large drusen
- Hypo-reflective drusen cores
- Hyper-reflective foci
- Reticular pseudodrusen
- Shallow, irregular RPE elevations (SIRE)
- Nascent geographic atrophy
- Pigmentary abnormalities

ERM

- Macular pseudohole
- Central bouquet
- Ectopic inner foveal layers
- Foveal pit
- Vitreoretinal adhesion
- Global adhesion
- Cotton ball sign
- Disorganisation of retinal inner layers (DRIL)

Group quiz and case discussions (60 mins)

In your tables of 8, participate in the slido quiz

Each table's team captain should submit one group response per question

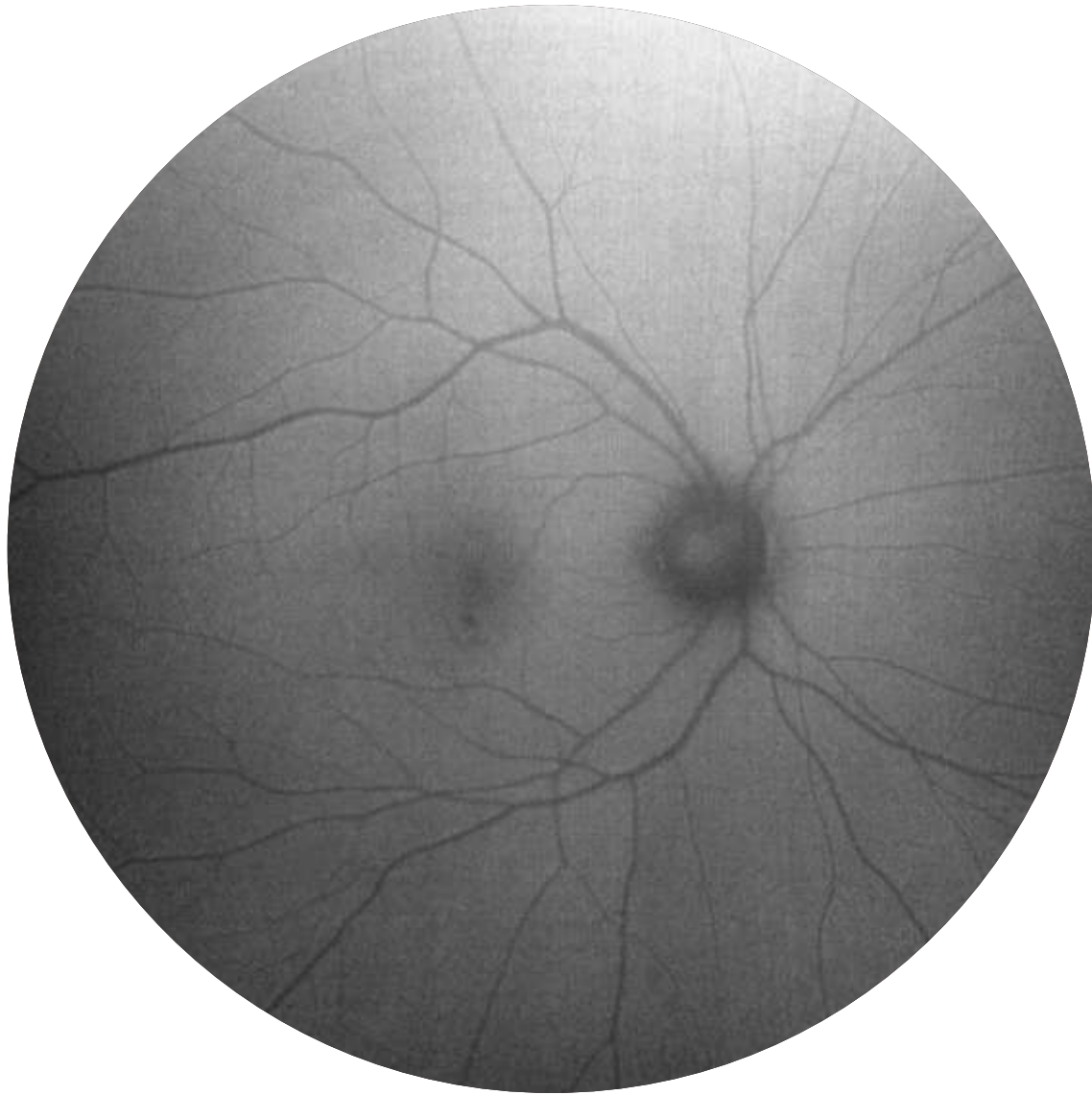
Case study 1: Seeing without looking

Diagnostic biomarkers of Central Serous Chorioretinopathy (CSCR)

Case study

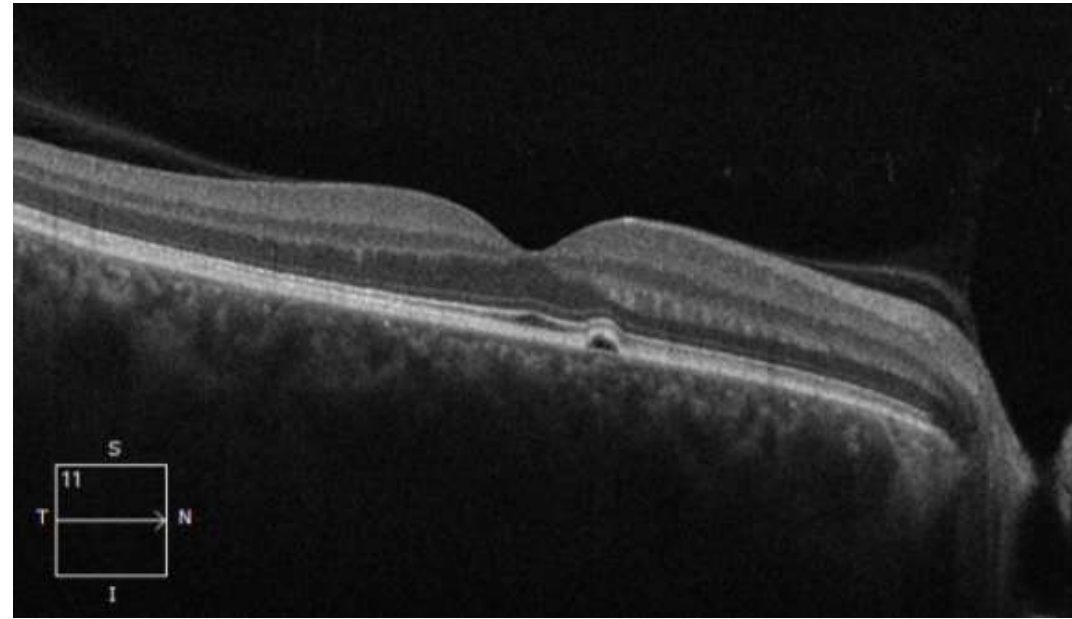
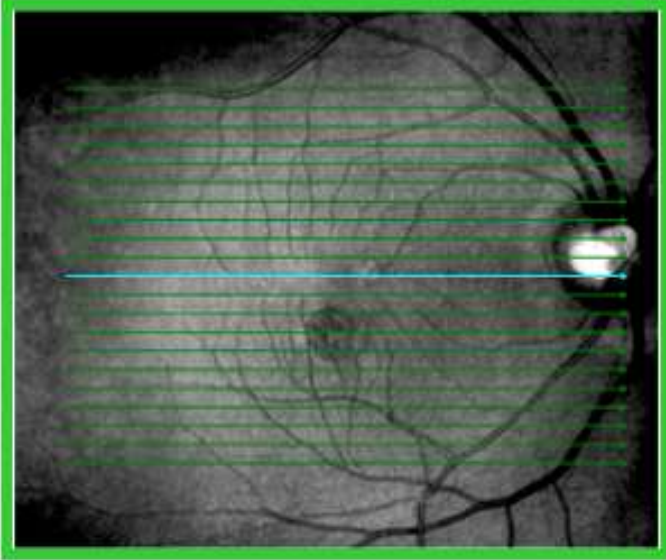
- 51yo male complaining of new onset difficulty reading OS
- Hx of previous CSCR OS 2019
- No flashes, floaters or metamorphopsia
- PMHx: Unremarkable

	OD	OS
Refraction	+1.50	+1.75
BCVA	6/4.8	6/9.5+1
Amsler grid	Unremarkable	Paracentral temporal blurred and wavy lines, + superior distortions



Scan Angle: 0°

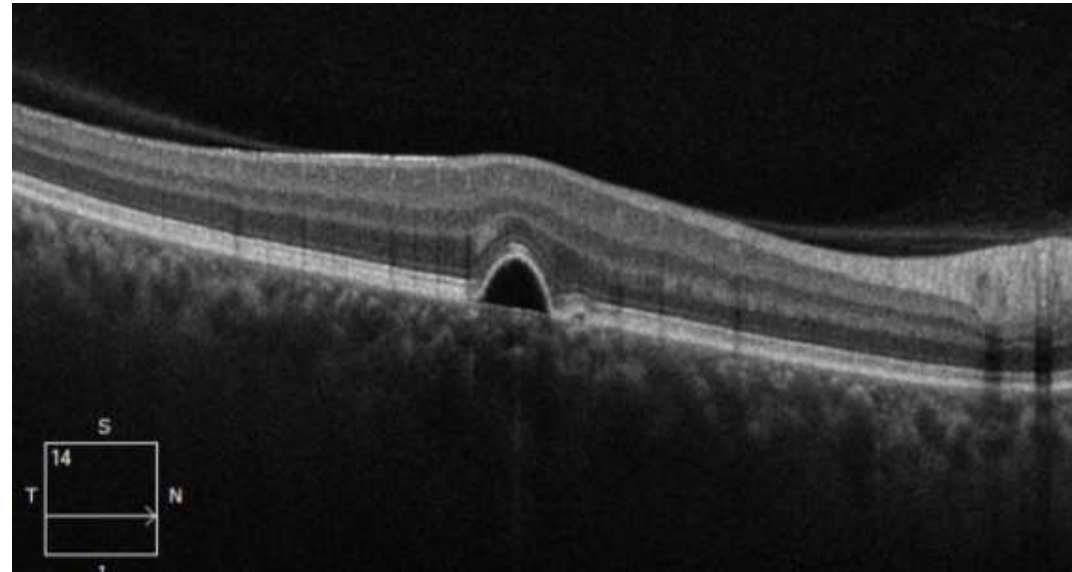
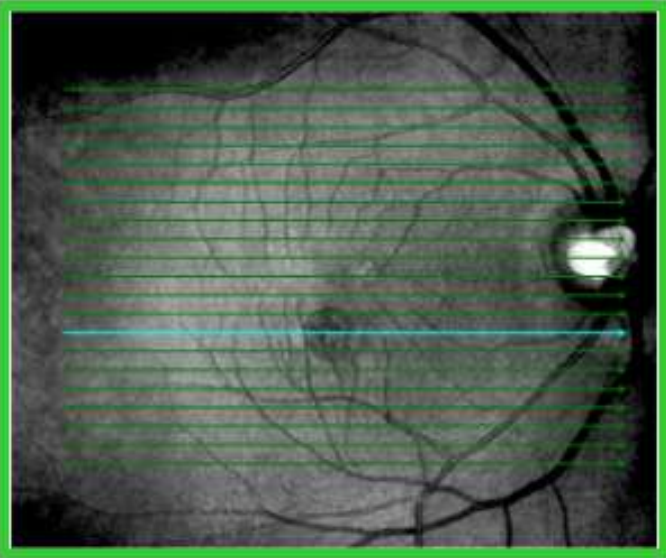
Spacing: 0.3 mm



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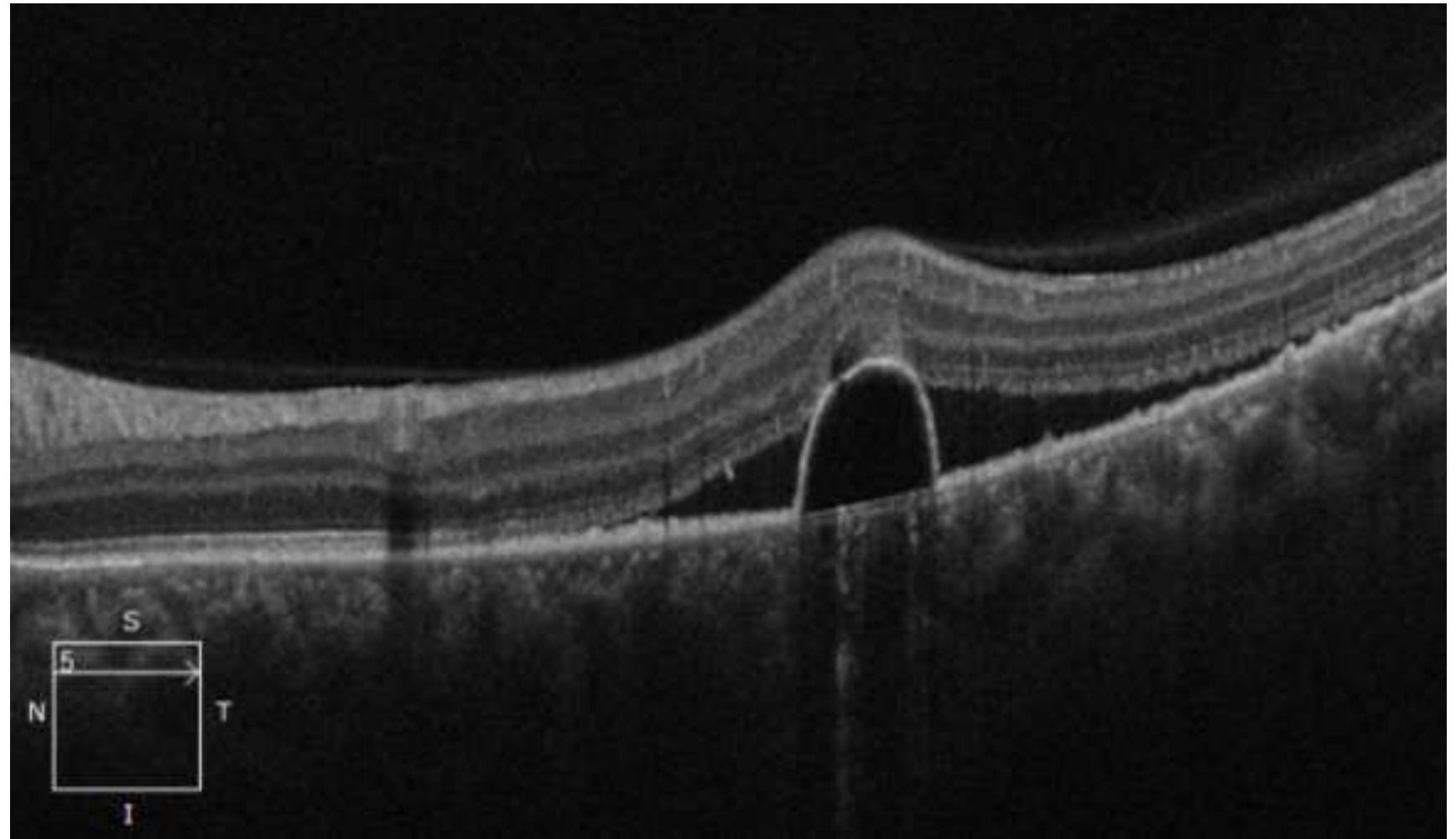
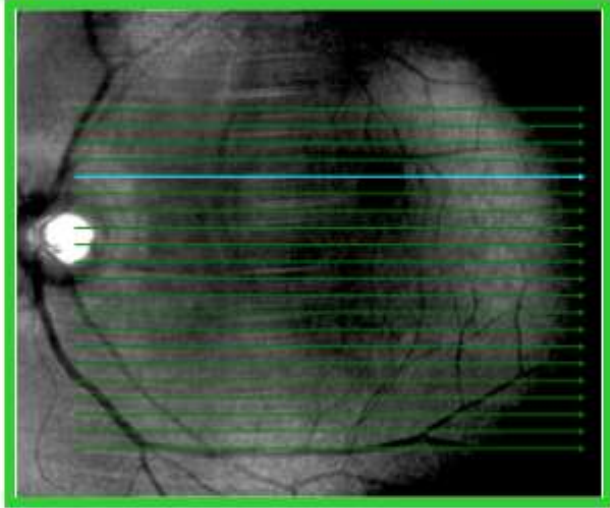
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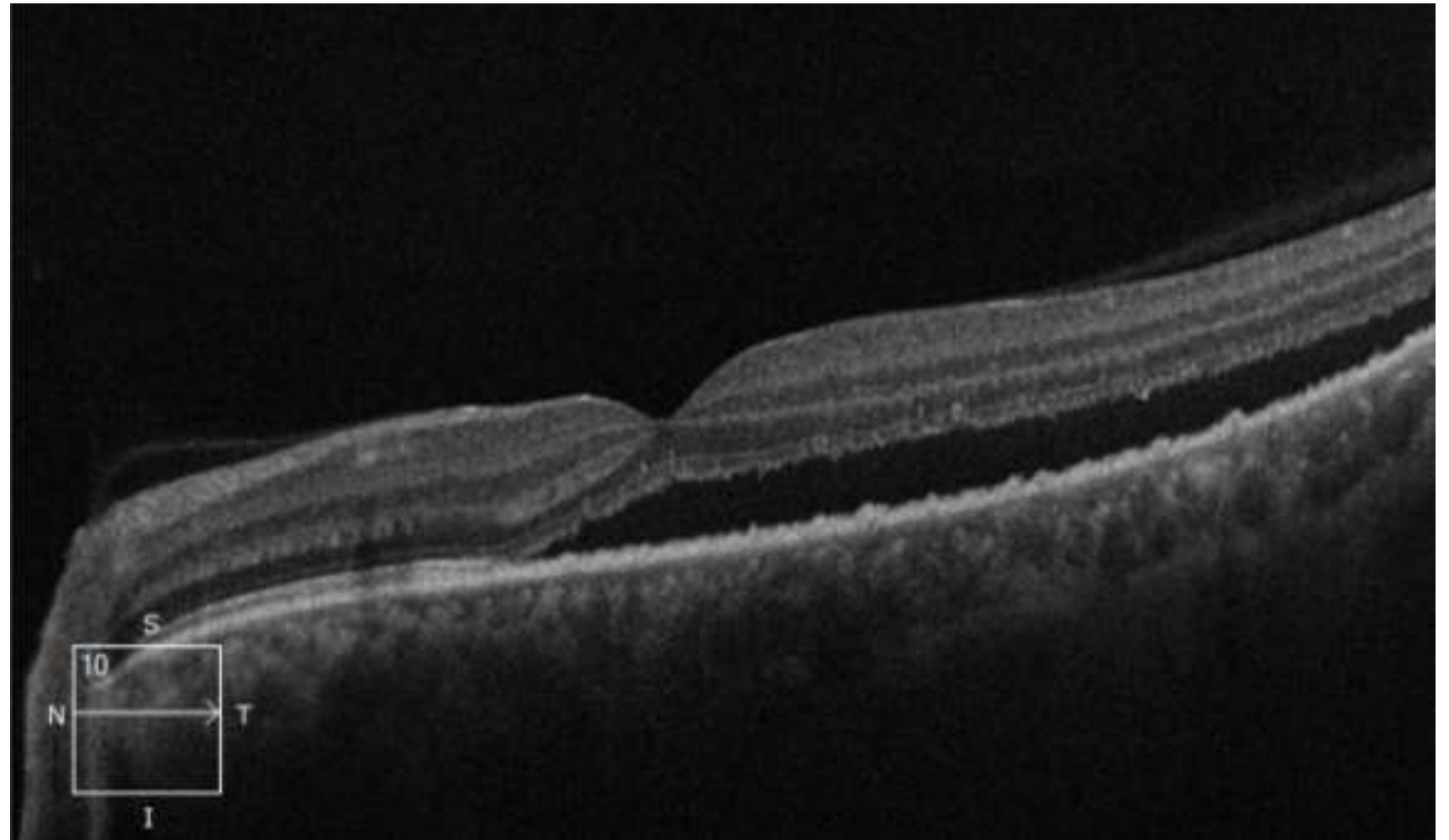
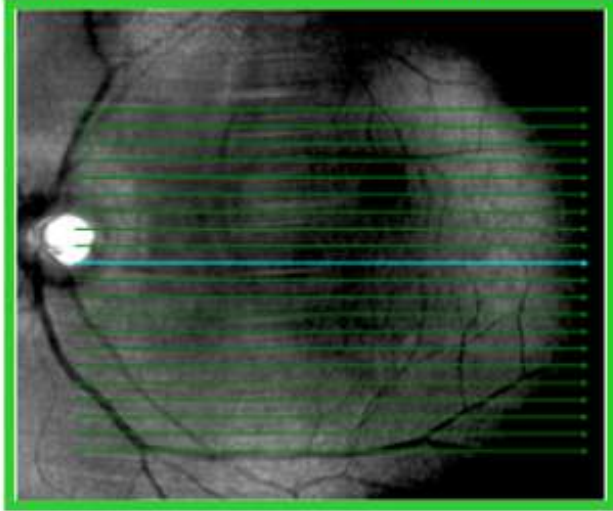


Images courtesy of the SOVS Optometry Clinic © 2025 University of New South Wales. All rights reserved.

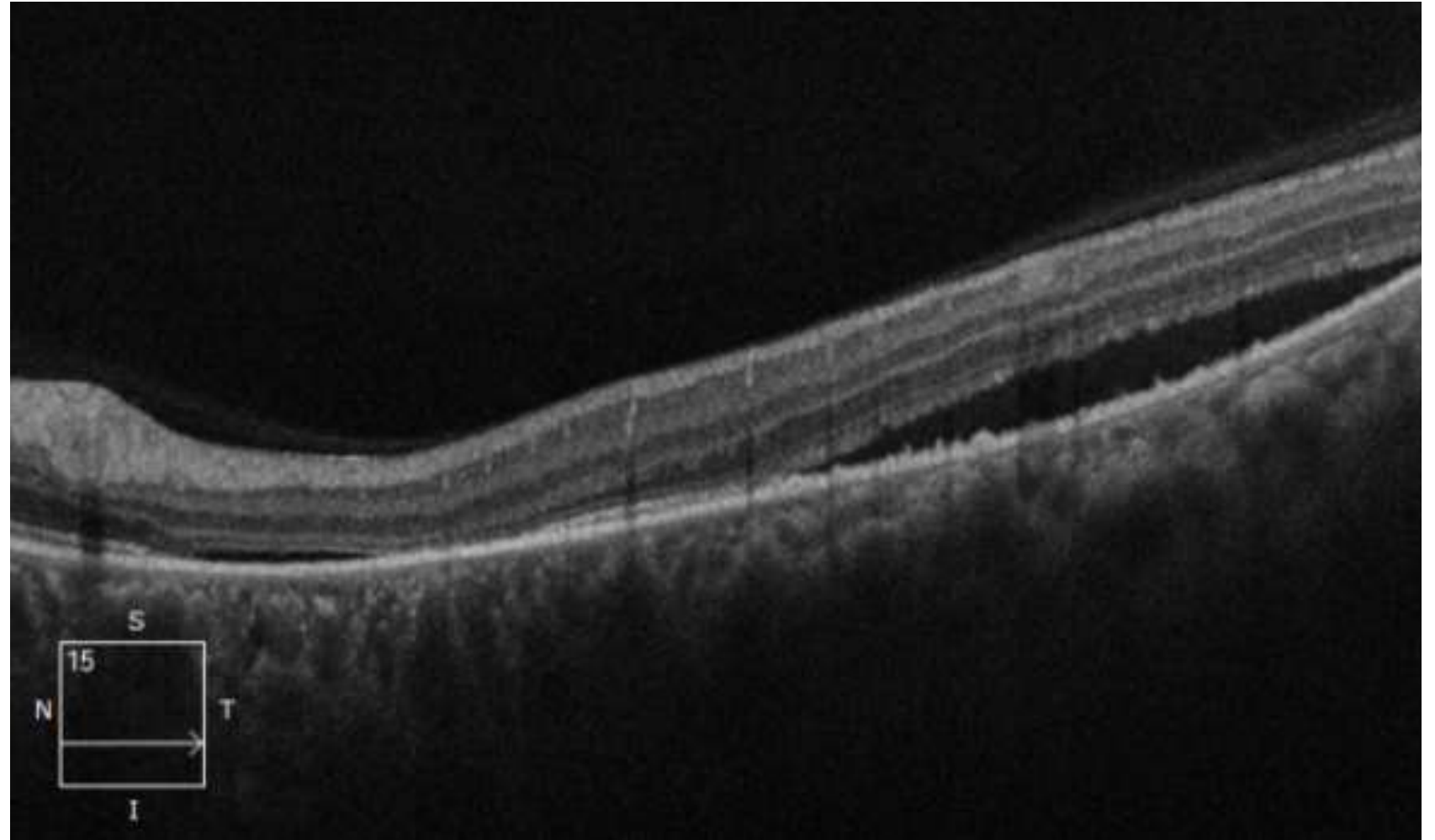
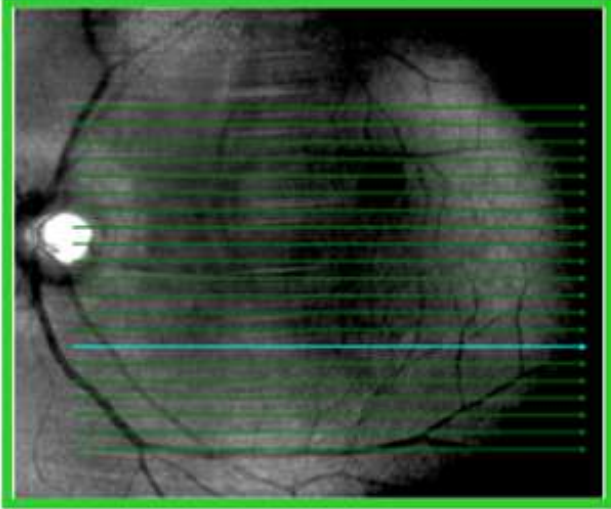
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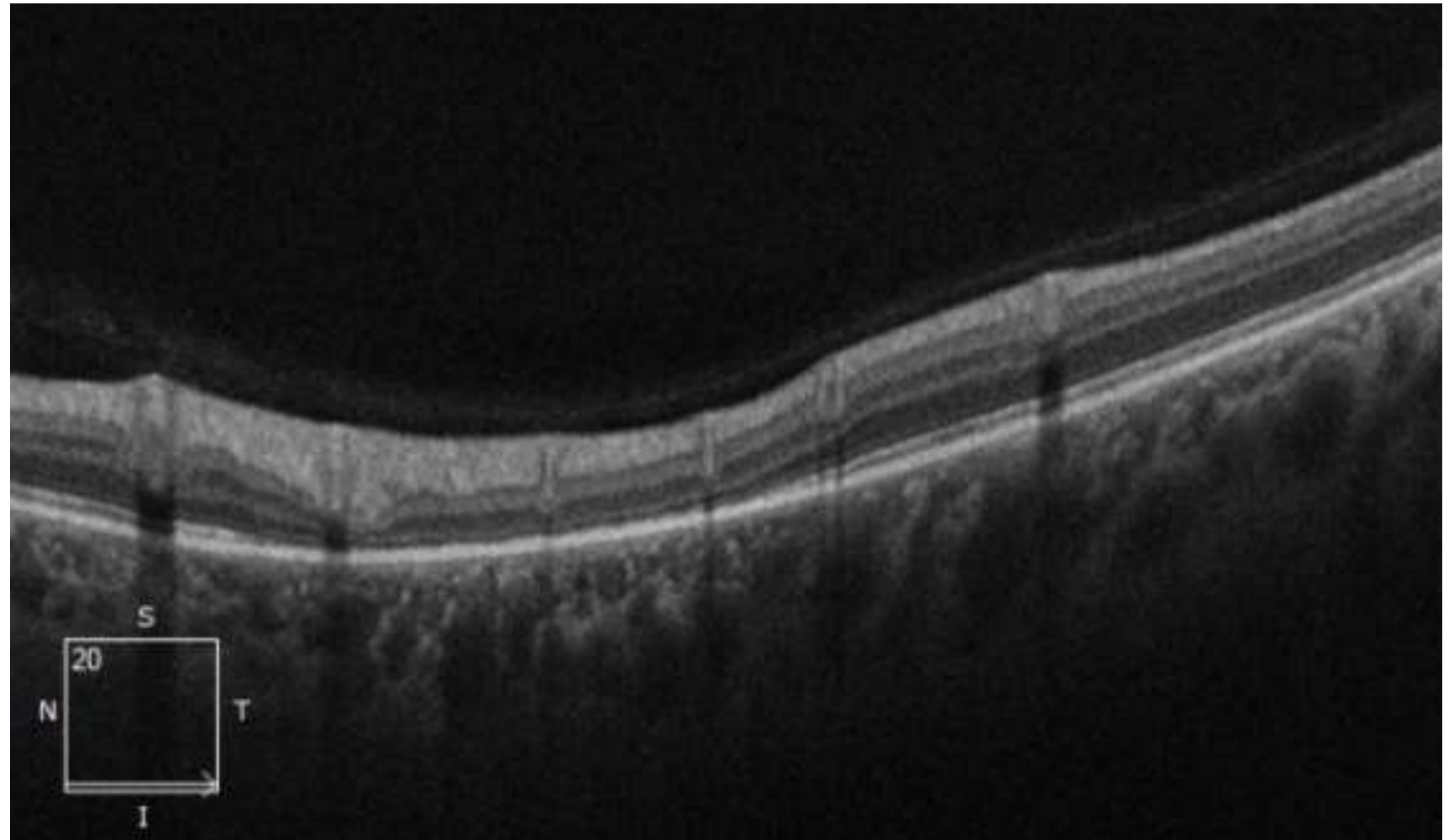
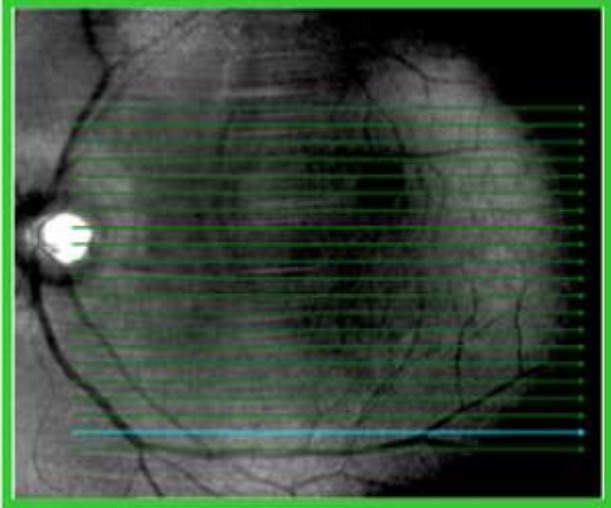
Scan Angle: 0° Spacing: 0.3 mm



Scan Angle: 0° Spacing: 0.3 mm

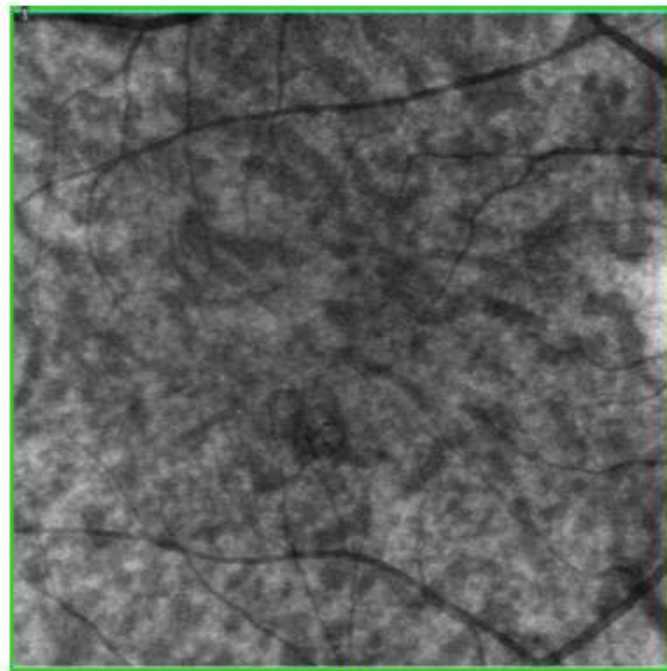


Scan Angle: 0° Spacing: 0.3 mm



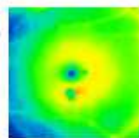
En Face Analysis : Angiography 6x6 mm

OD OS

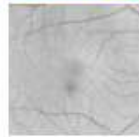


Choroidal: Offset = 72 μ m Thickness = 154 μ m

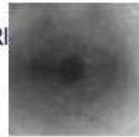
Thickness Map



OCT Fundus



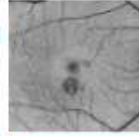
VRI



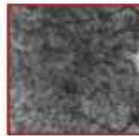
Mid-Retina



IS/OS-Ellipsoid



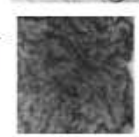
Choroid



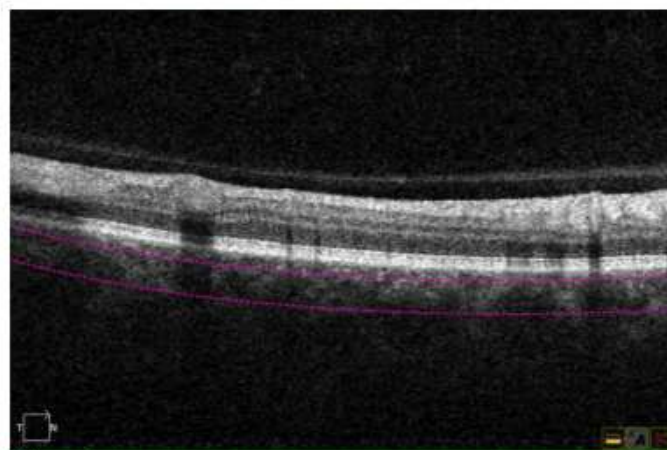
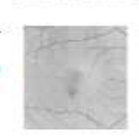
Minimum Intensity



Custom - (Choroidal)



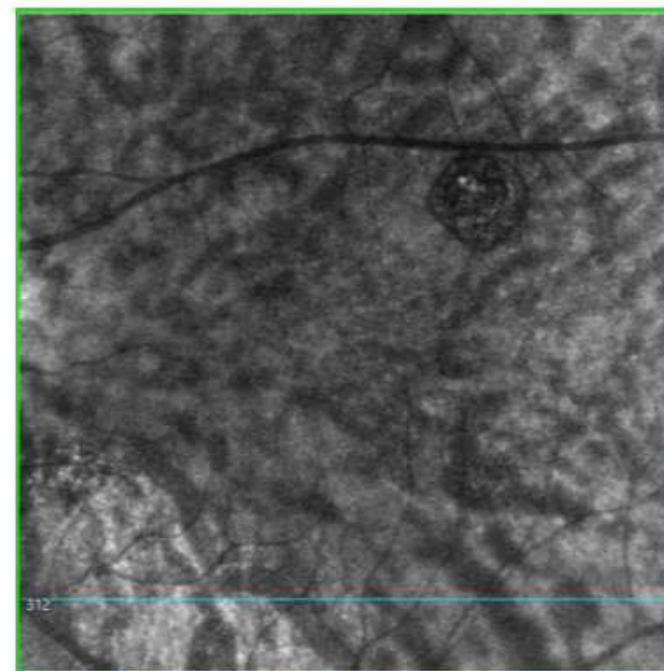
Custom - (OCT Fundus)



Slice: 1

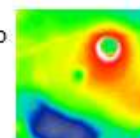
En Face Analysis : Angiography 6x6 mm

OD OS

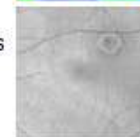


Custom - (Choroidal): Offset = 116 μ m Thickness = 172 μ m

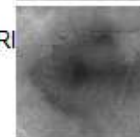
Thickness Map



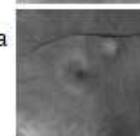
OCT Fundus



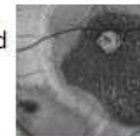
VRI



Mid-Retina



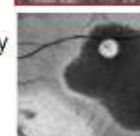
IS/OS-Ellipsoid



Choroid



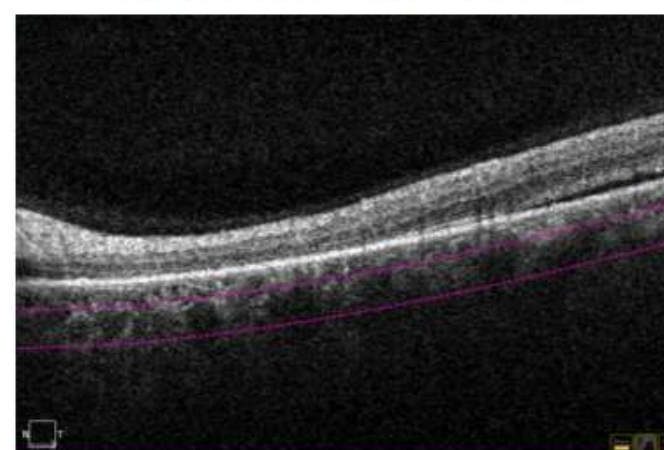
Minimum Intensity



Custom - (Choroidal)



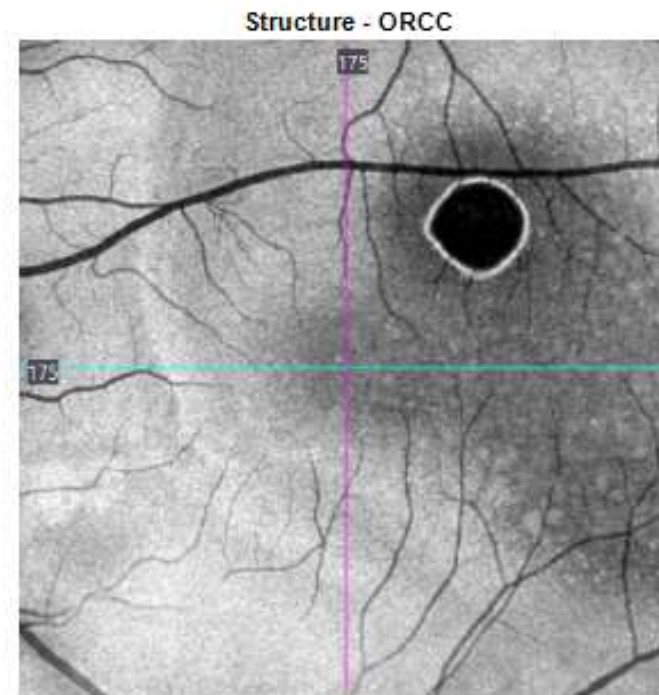
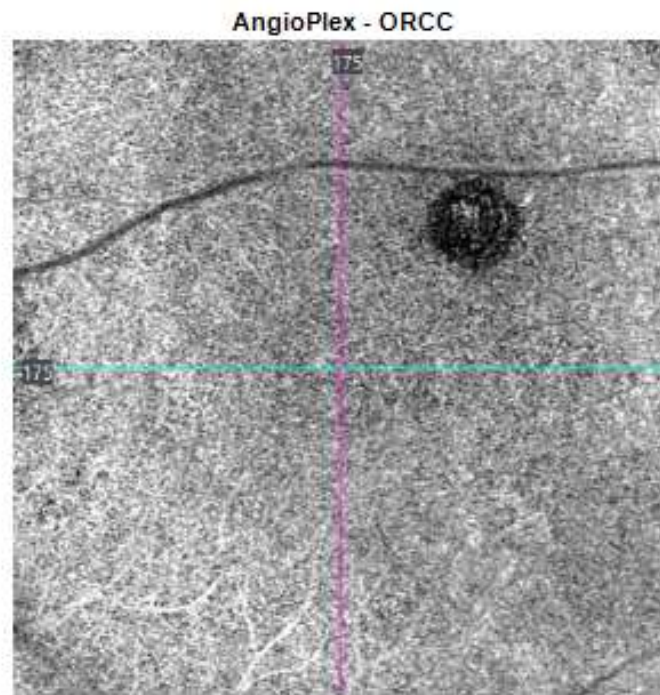
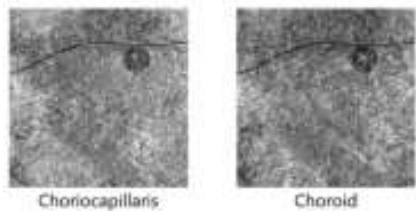
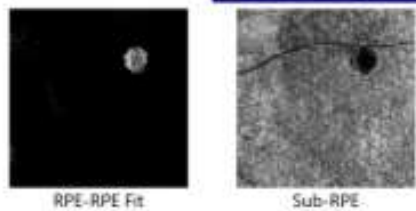
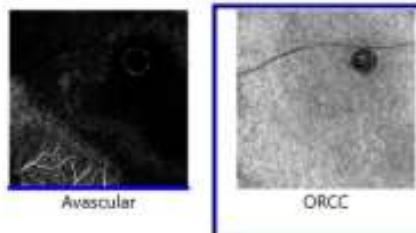
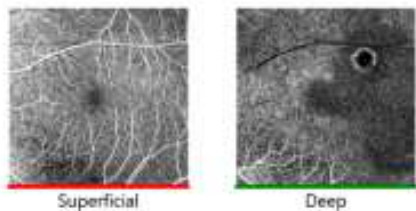
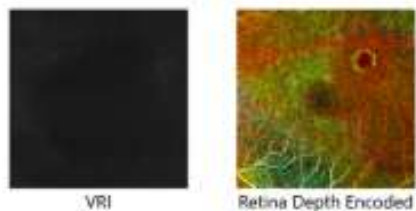
Custom - (OCT Fundus)



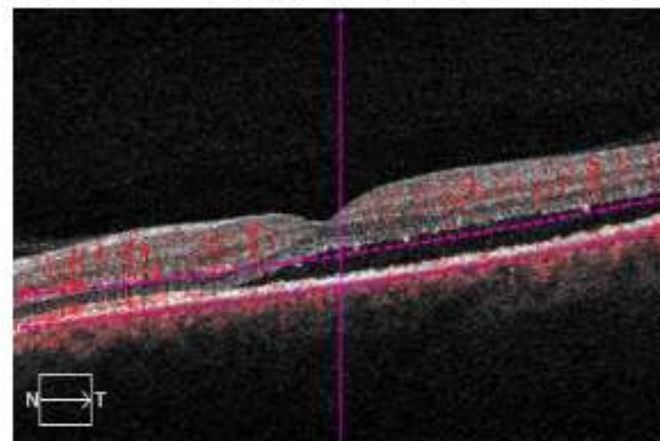
Slice: 312



What biomarkers are evident in the en face OCT image reports presented? Check all that apply

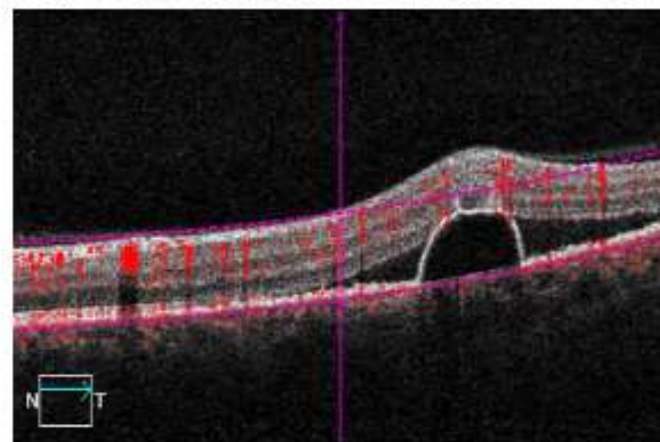
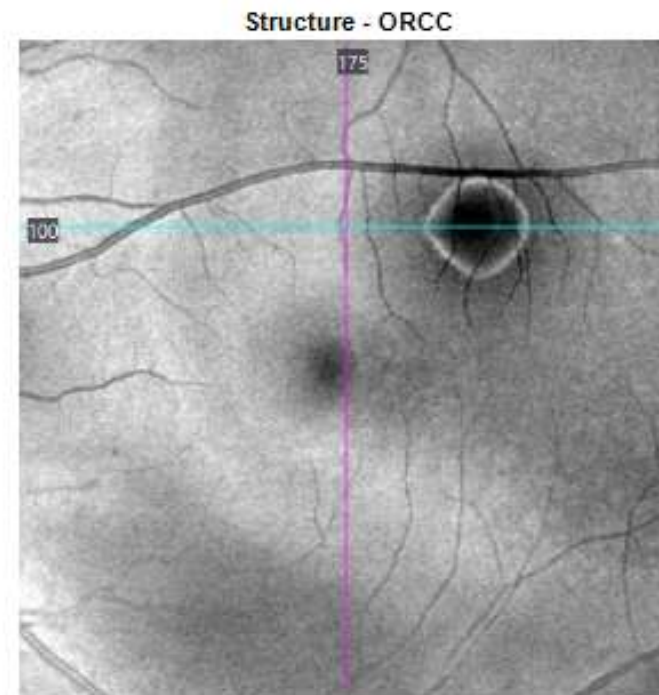
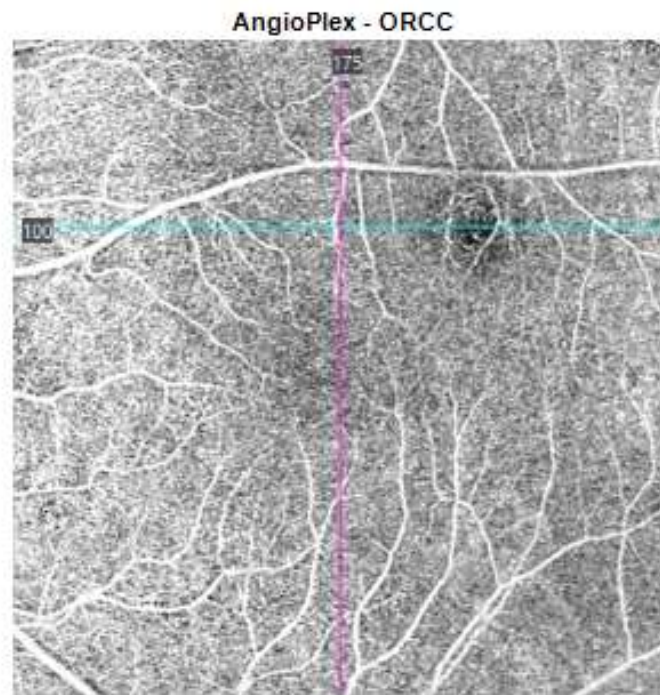
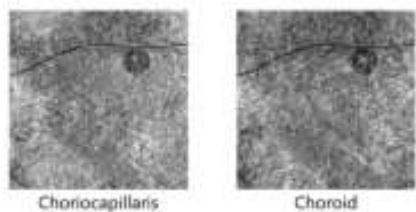
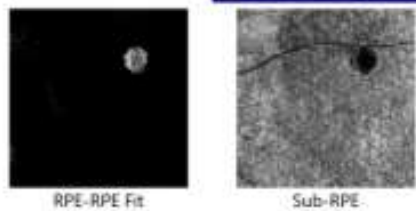
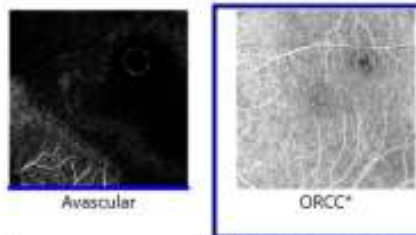
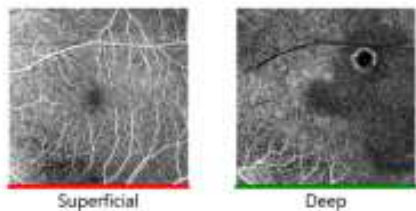
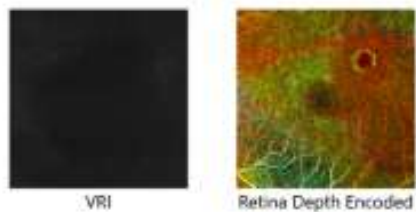


Overlays
Structure - None
AngioPlex - None



Slice: 175

Tracked during scan ✓



Overlays
Structure - None
AngioPlex - None

Slice: 100

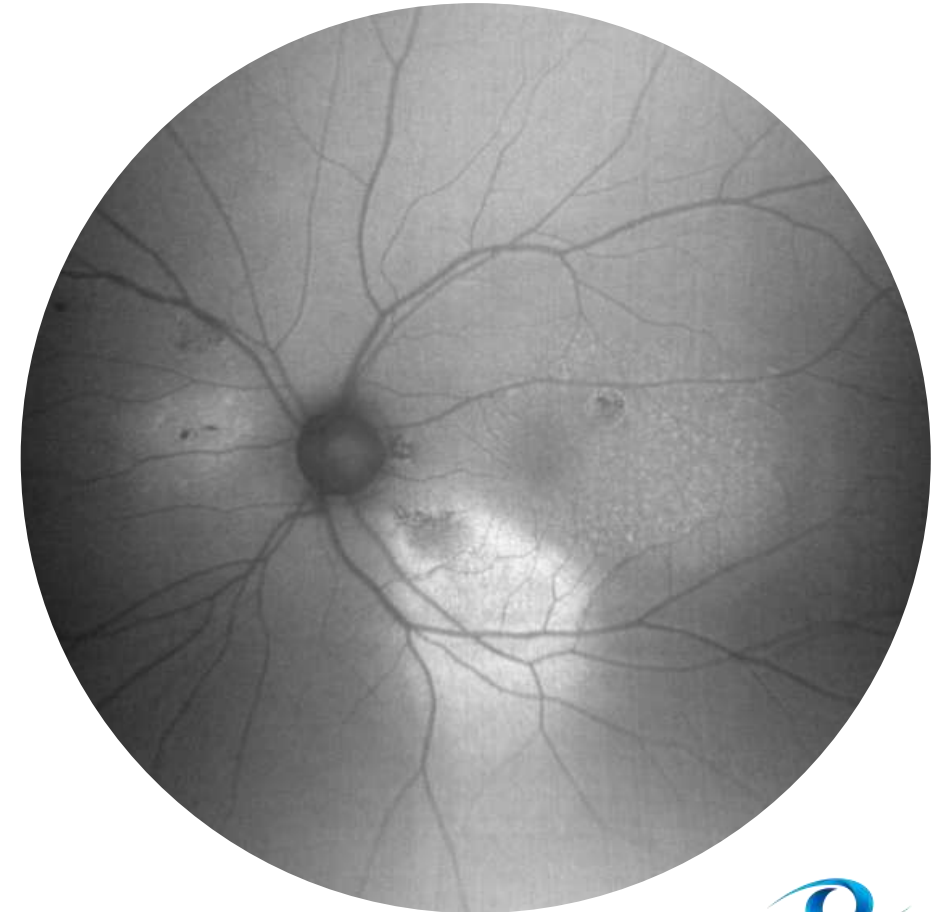
Tracked during scan ✓



Which of the following should the patient be carefully assessed for because if present might signify macular neovascularisation? Check all that apply

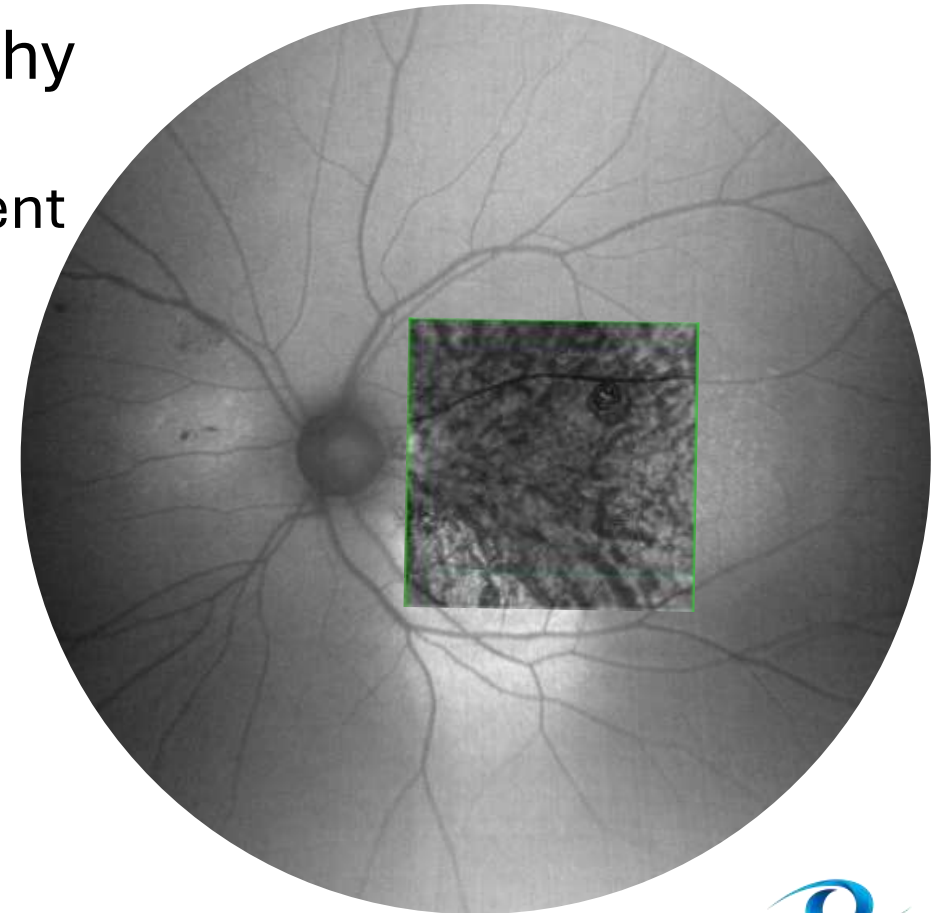
Case analysis (without consideration of biomarkers)

- Dx: serous PEDs OU, serous retinal detachment OS, widespread retinal pigment epitheliopathy OS
 - Recurrent CSCR?
- Mgmt: Refer to ophthalmologist
 - For a second opinion
 - To rule out other causes or macular SRF



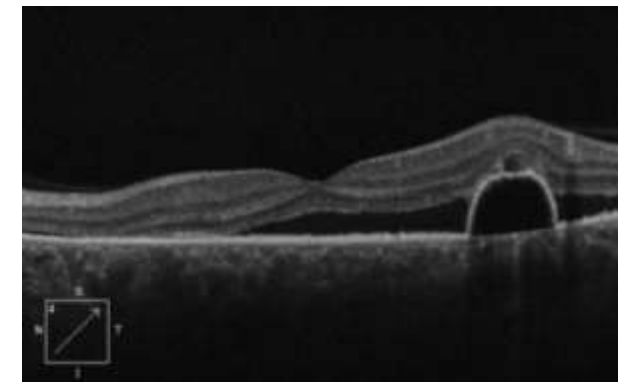
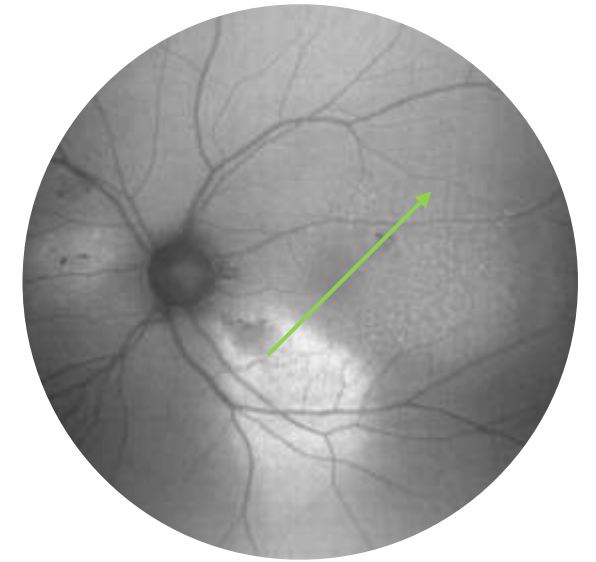
Case analysis (with consideration of biomarkers)

- Dx: Pachychoroid pigment epitheliopathy OD, recurrent active CSCR OS
 - Serous PEDs OU, serous retinal detachment OS, widespread retinal pigment epitheliopathy OS
 - Pachyvessels, increased choroidal thickness, inner choroid attenuation OU
 - No FIPED or signs of MNV either eye
 - Acute SRF likely self-resolving
- Mgmt: Review 6-weeks
 - Interim Amsler grid self-monitoring
 - Px education wrt risk factors



Central serous chorioretinopathy

- Chorioretinal condition characterised by serous retinal detachment in the active stage
 - Most commonly at the macula
 - Usually associated with PEDs, RPE dysfunction
- Caused by choroidal hyperpermeability
 - Venous overload of the choroidal circulation
 - Increased scleral thickness



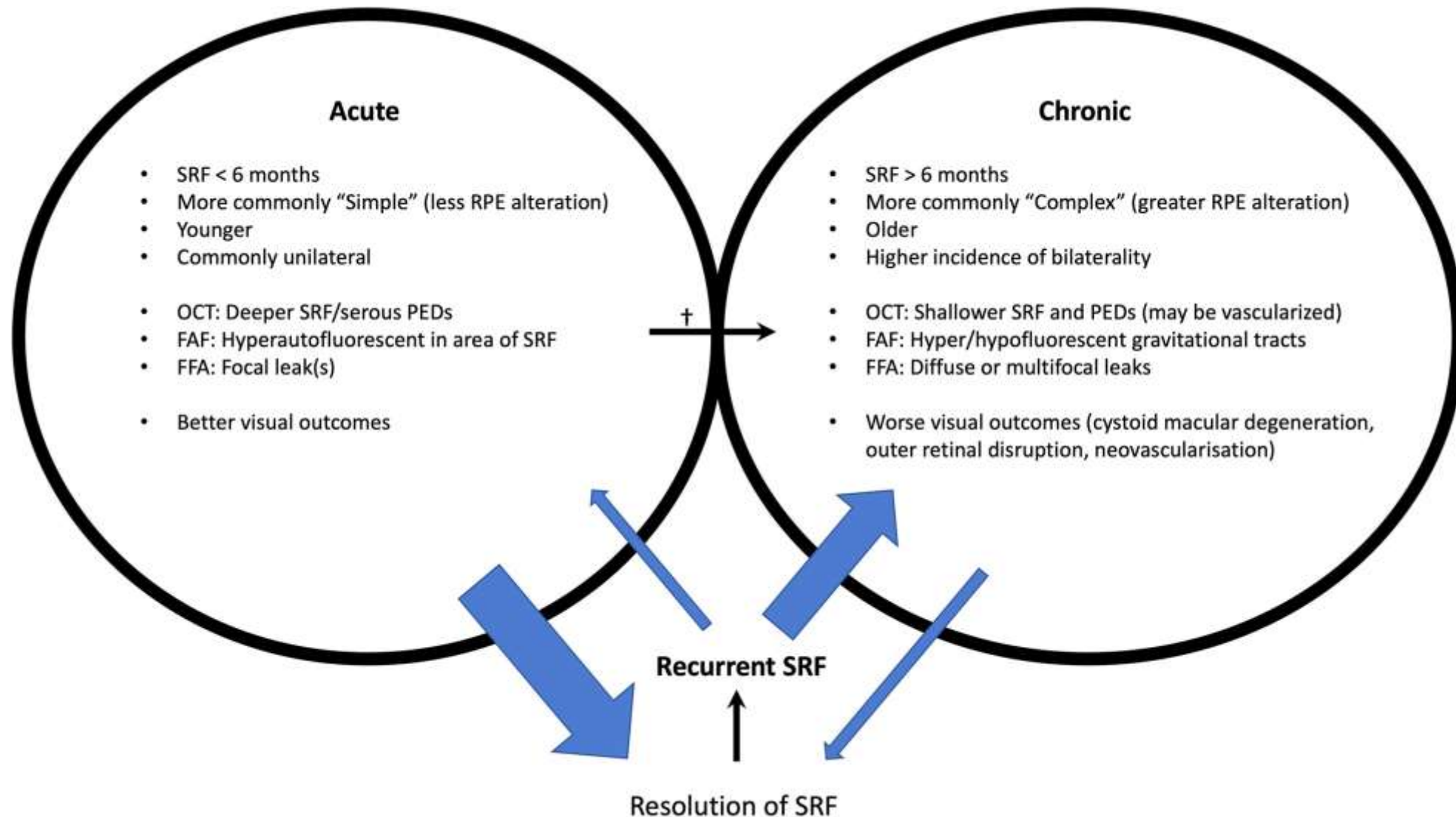
Central serous chorioretinopathy



- Commonly affects males aged 20-50 years
- Higher prevalence in Asian populations
 - 27 per 100 000 men and 15 per 100 000 women in Taiwan
- Older patients are more likely to have diffuse retinal pigment epitheliopathy, bilateral disease, and MNV
- Acute symptoms: central scotoma, metamorphopsia, dyschromatopsia, micropsia, hypermetropisation and reduced contrast sensitivity

Diagnosis

- Absence of the normal foveal reflex
- Serous retinal detachment at the fovea
 - Usually clear, with possible fibrinous deposits
 - Gravitational tracts/tracks
- PED, RPE atrophy, hyper- and hypo-pigmentary abnormalities
- May be categorised as acute, chronic, recurrent, simple or complex



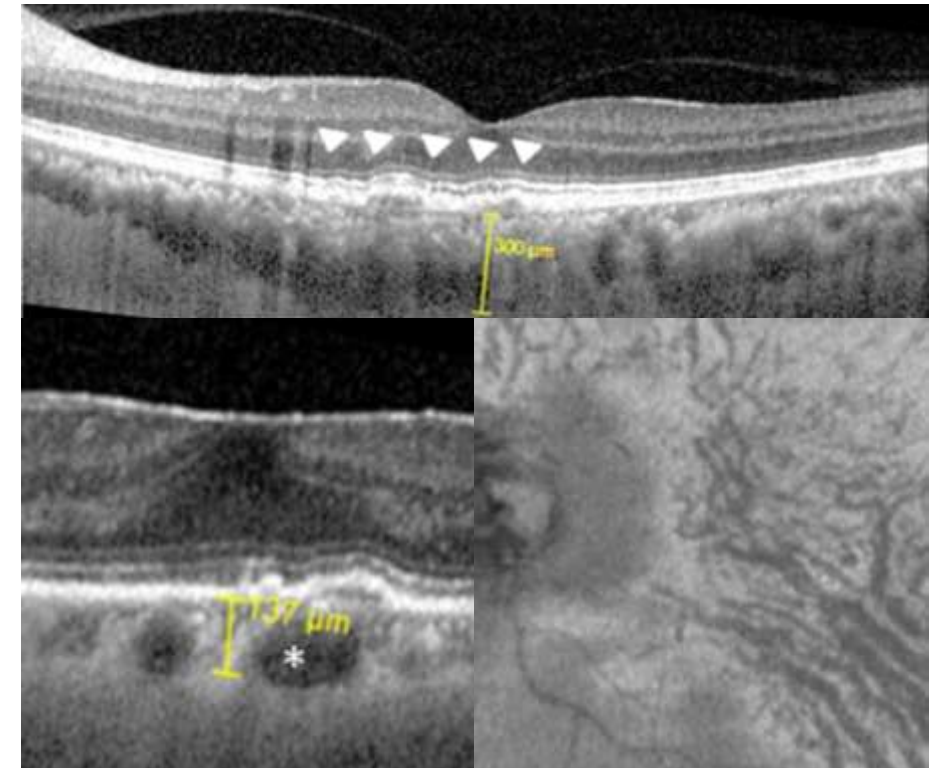
Top three differential diagnoses of active/acute CSCR

- Retinal vascular disease
- Neovascular AMD
- Inflammatory diseases

Key question: How can I confidently rule out other causes of serous retinal detachment?

Choroidal features common to pachychoroid disease

- Aka diagnostic biomarkers
- Focal or diffuse increase in **choroidal thickness (CT)**
 - Subfoveal CT >300 μm
 - Extrafoveal focus of increased CT, exceeding subfoveal CT by 50 μm
- **Pachyvessels**: dilated choroidal vessels in Haller's layer that do not taper toward the posterior pole
 - Largely responsible for increased CT, though may be masked by overlying choriocapillaris and Sattler's layer thinning (**inner choroid attenuation**)

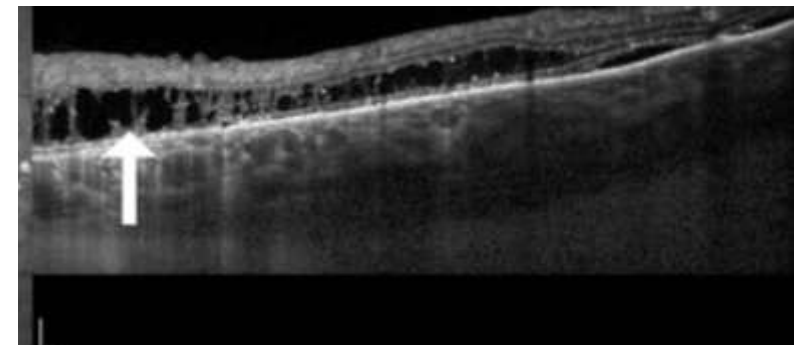
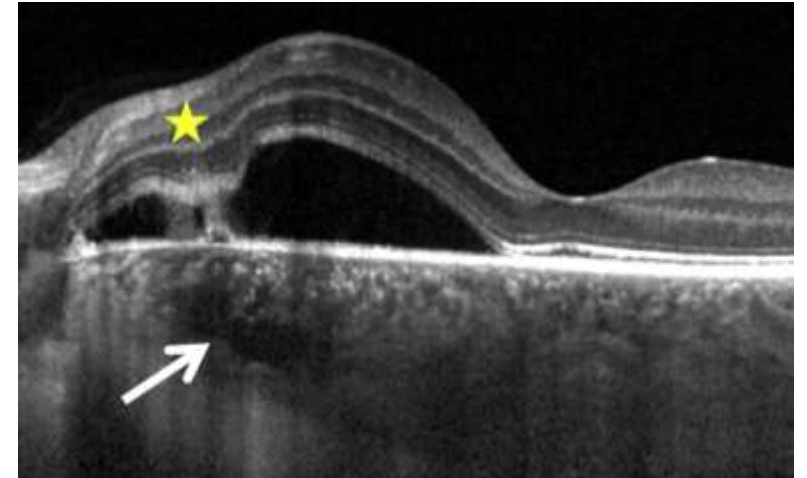




Where are pachyvessels typically located?

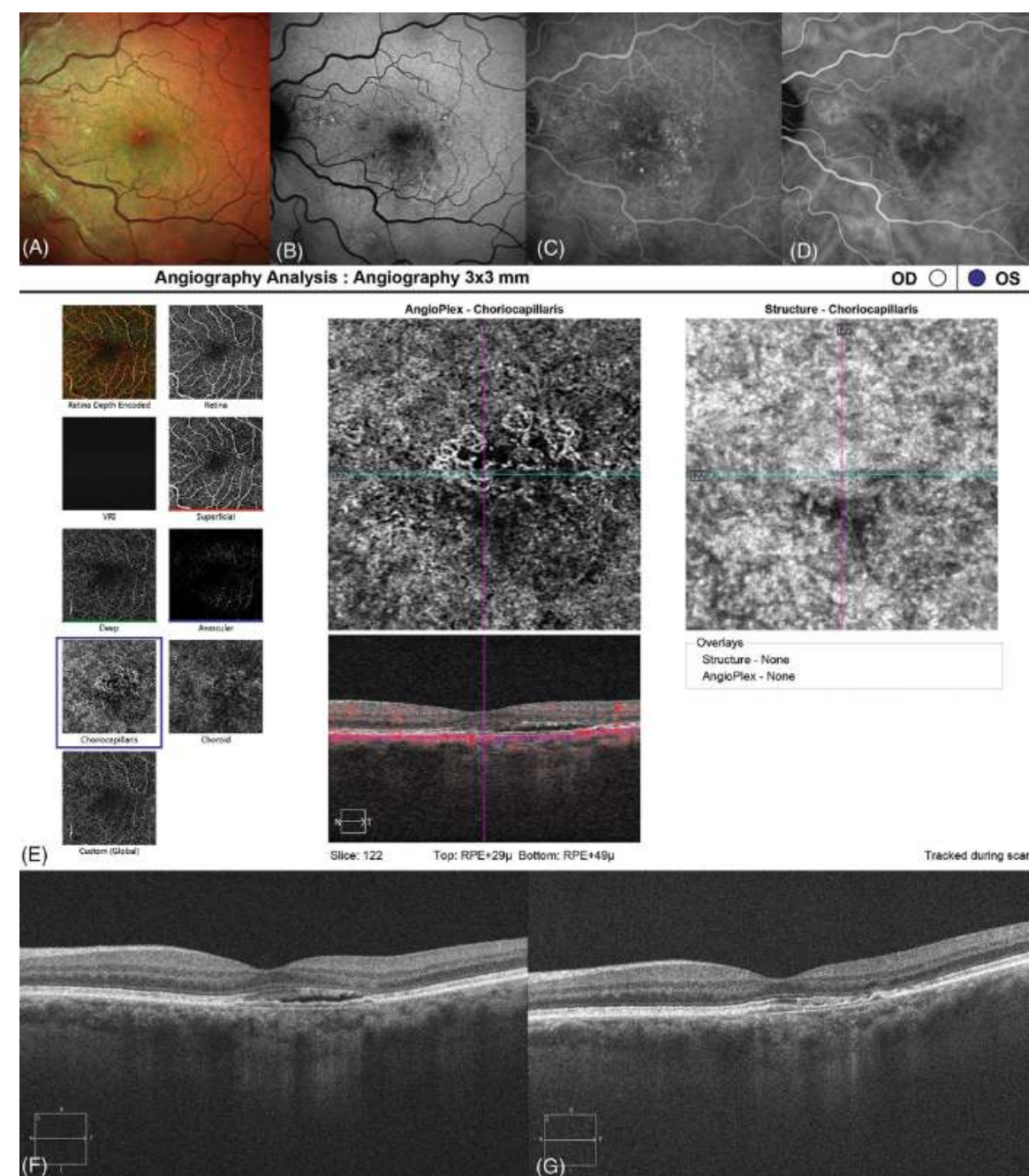
Staging biomarkers of CSCCR

- Well-defined serous retinal detachment with or without serous PED
- Over time:
 - Elongated photoreceptor outer segments + subretinal fibrin, intraretinal lipid deposition and subretinal yellowish deposits (**hyper-reflective foci**) indicate persistence of SRF
 - Retinal detachment becomes shallower and broader with attenuation and sagging/'**dipping**' of outer retinal layers
 - **Cystoid macular degeneration** may develop (prognostic for poor visual outcome)



FIPED

- Also known as the double layer sign, non-specific sign denoting a split between the RPE and Bruch's membrane, that may indicate type 1 macular neovascularisation.
- “Whilst almost all eyes with CNV secondary to CSC have FIPEDs only 22.7% of FIPEDS are vascularised.”



Management

- Observe for spontaneous resolution and complications:
 - RPE and/or photoreceptor atrophy
 - Secondary MNV
- Avoid modifiable risk factors at presentation and lifelong
 - Cessation, avoidance or minimisation of corticosteroids if possible via GP
 - ‘Treat’ systemic HTN, stress, sleep apnoea, *Helicobacter pylori* infection
- Consider referring for Tx highly symptomatic, persistent, recurrent or complex cases

Future applications

- Refined staging biomarkers of acute vs chronic CSCR, other pachychoroid spectrum disease and emergence of NV
- Prognostic biomarkers associated with **episode persistence** (need to treat), **recurrence**, or **poor visual outcomes**
- Predictive biomarkers of treatment response



AI generated using MS Co-pilot

Key points for case study 1: Seeing without looking

- Diagnostic biomarkers are useful for differential diagnosis and typically relate to the underlying disease pathophysiology
- In cases of suspected active pachychoroid spectrum disease, assess the underlying RPE and choroid

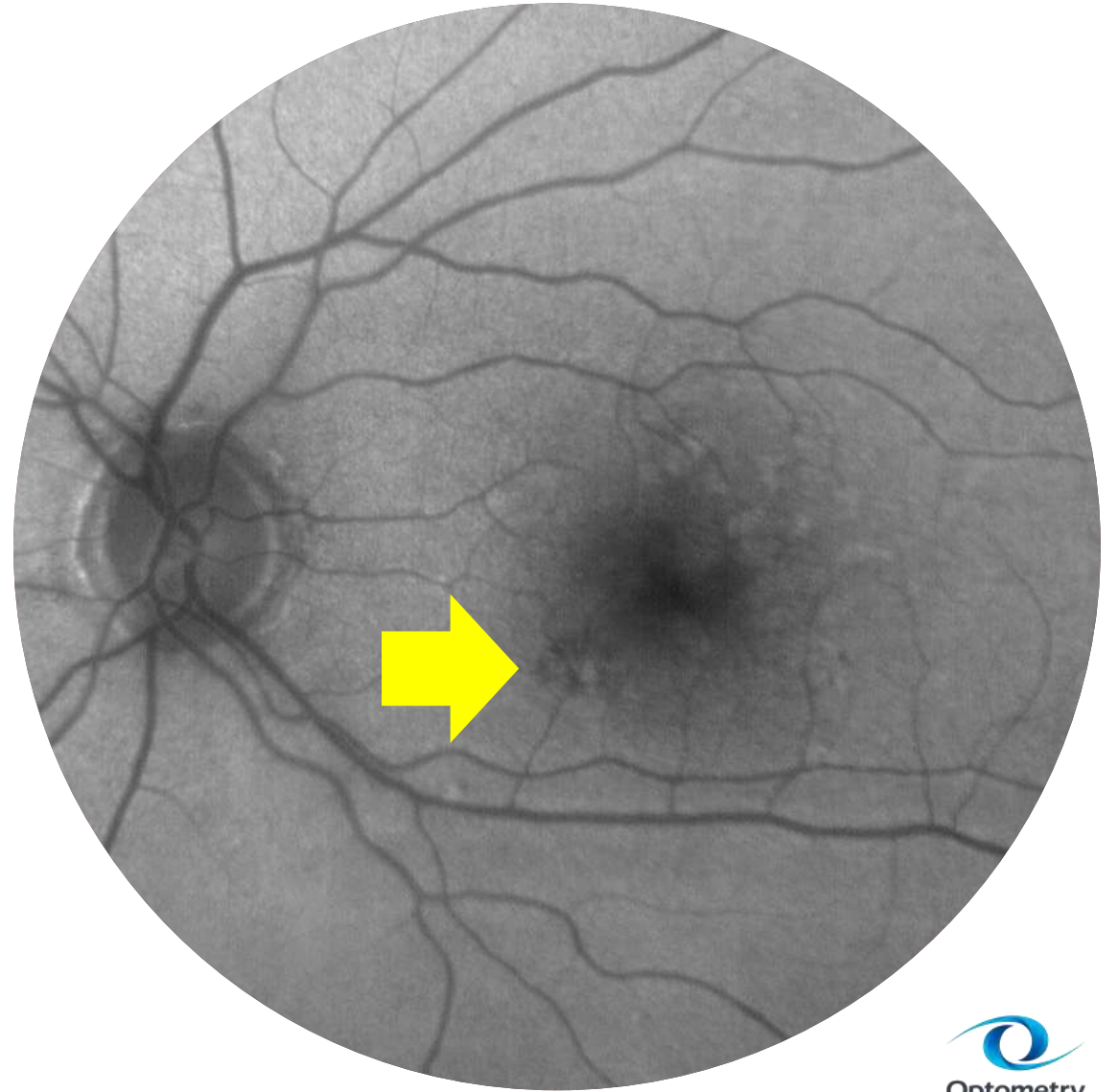
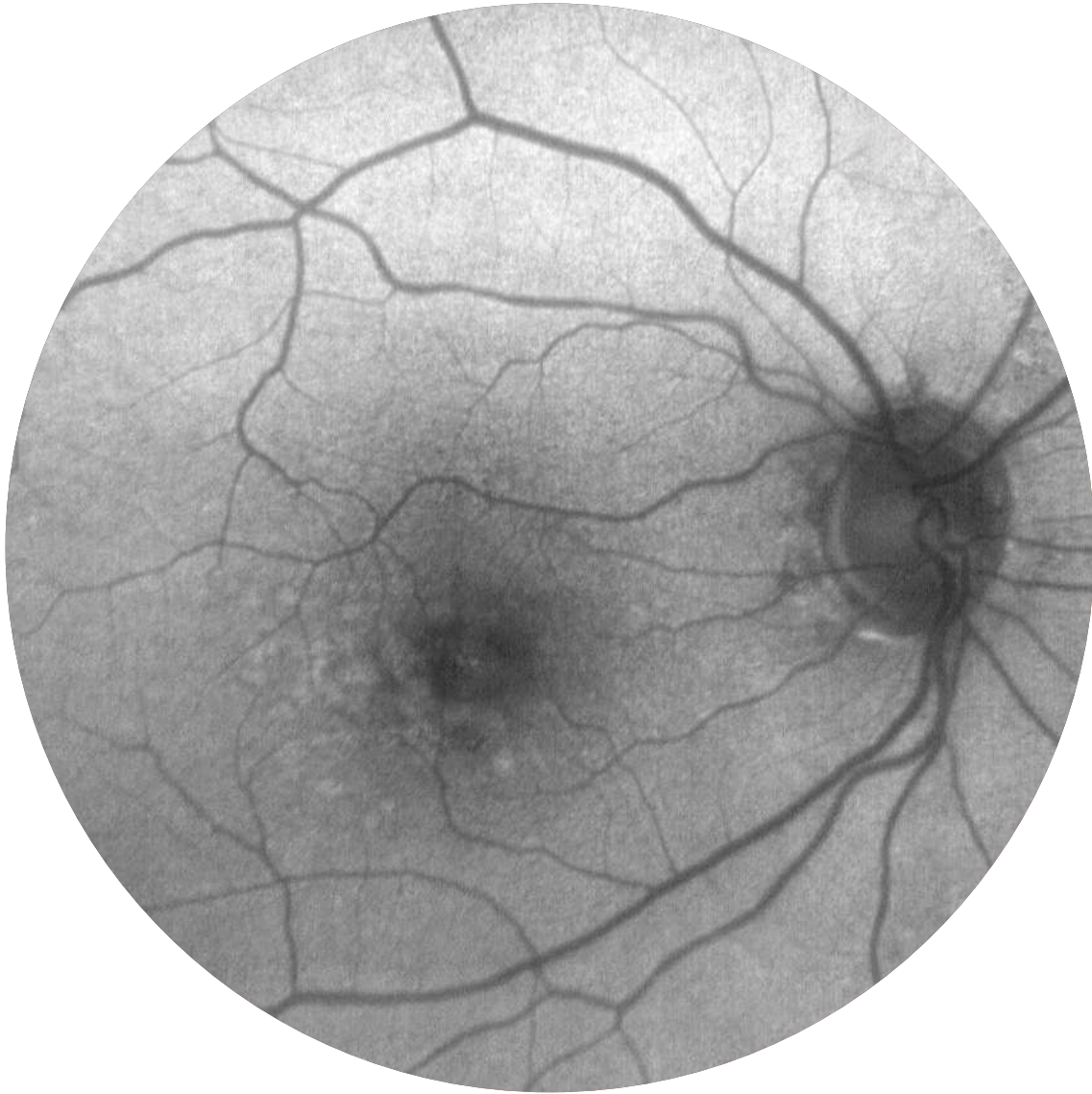
Once you see it, you can't unsee it

Prognostic biomarkers in AMD

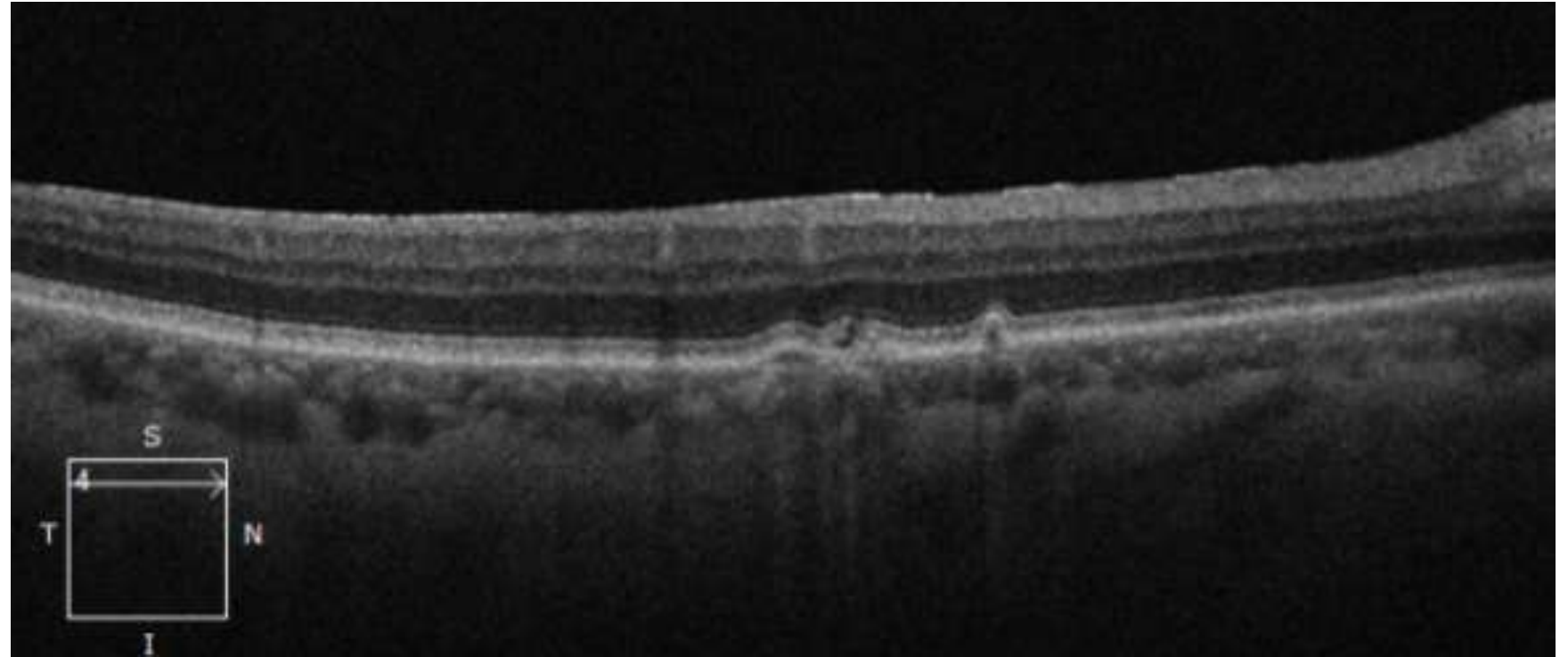
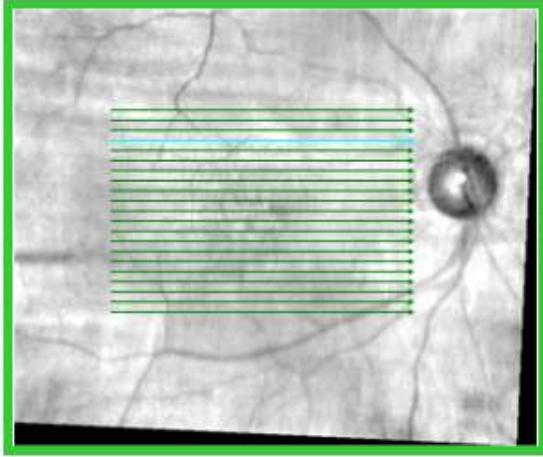
Case study

- Asymptomatic 81yo male
- Presented for an annual AMD review
- Longstanding floaters, no flashes or metamorphopsia
- Checks Amsler grid daily, Macutec once daily
- PMHx: High cholesterol, HTN, former smoker

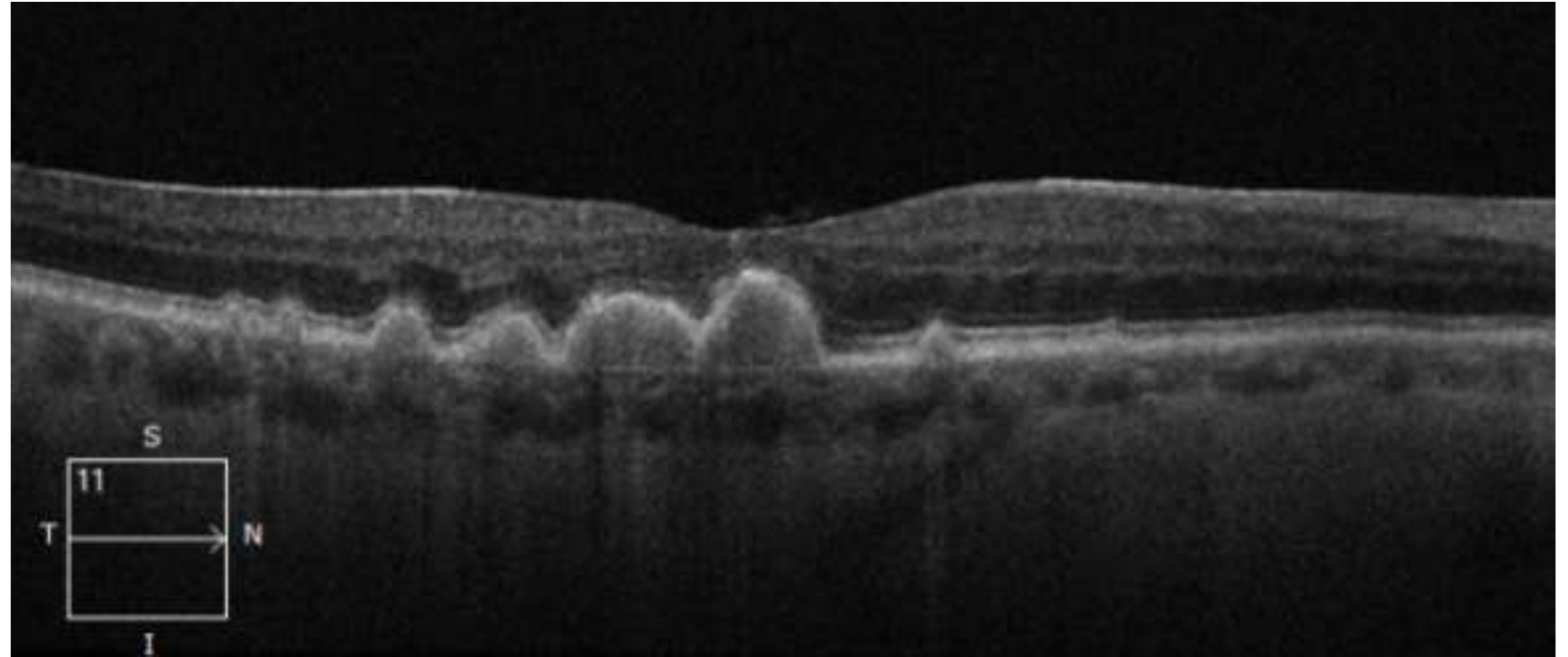
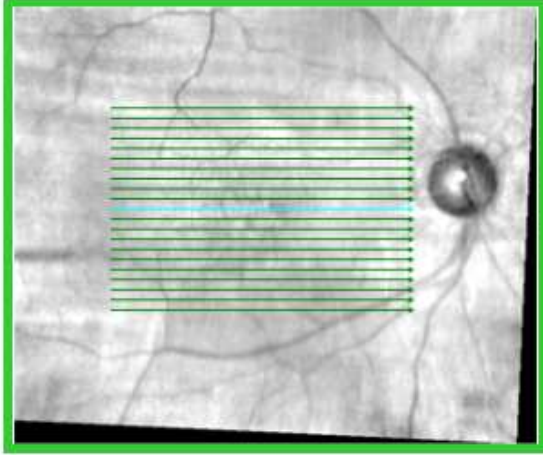
	OD	OS
Refraction	-0.25/-0.25x135	Pl/-0.50x60
BCVA	6/9.5-2	6/6-2
Amsler grid	Unremarkable	Unremarkable



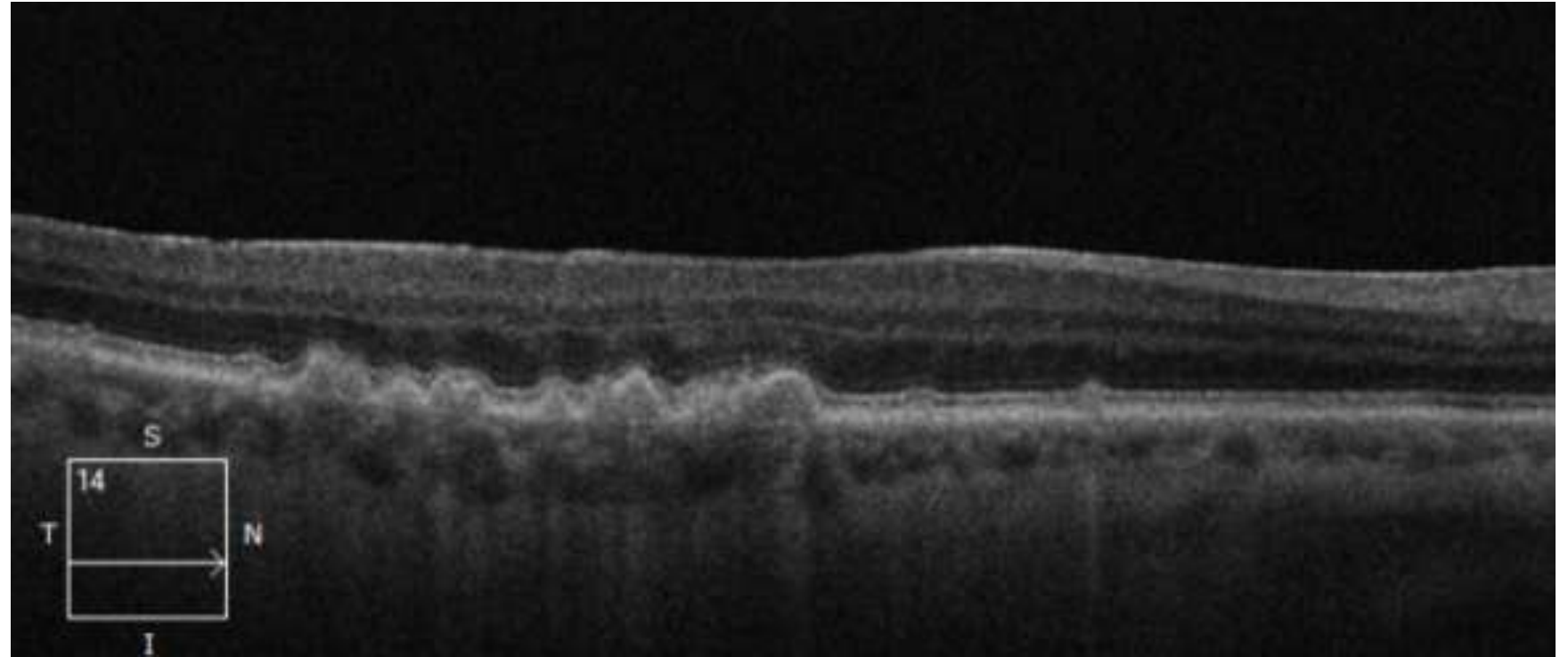
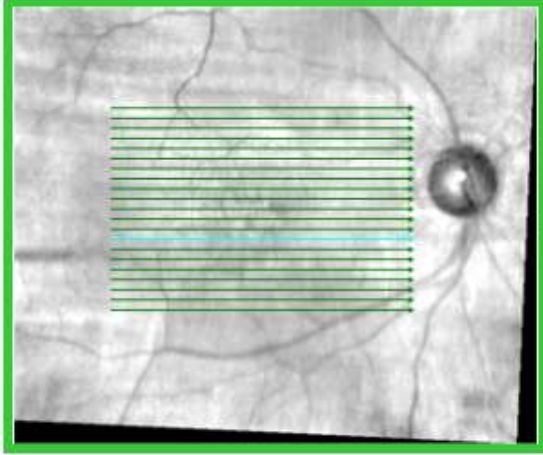
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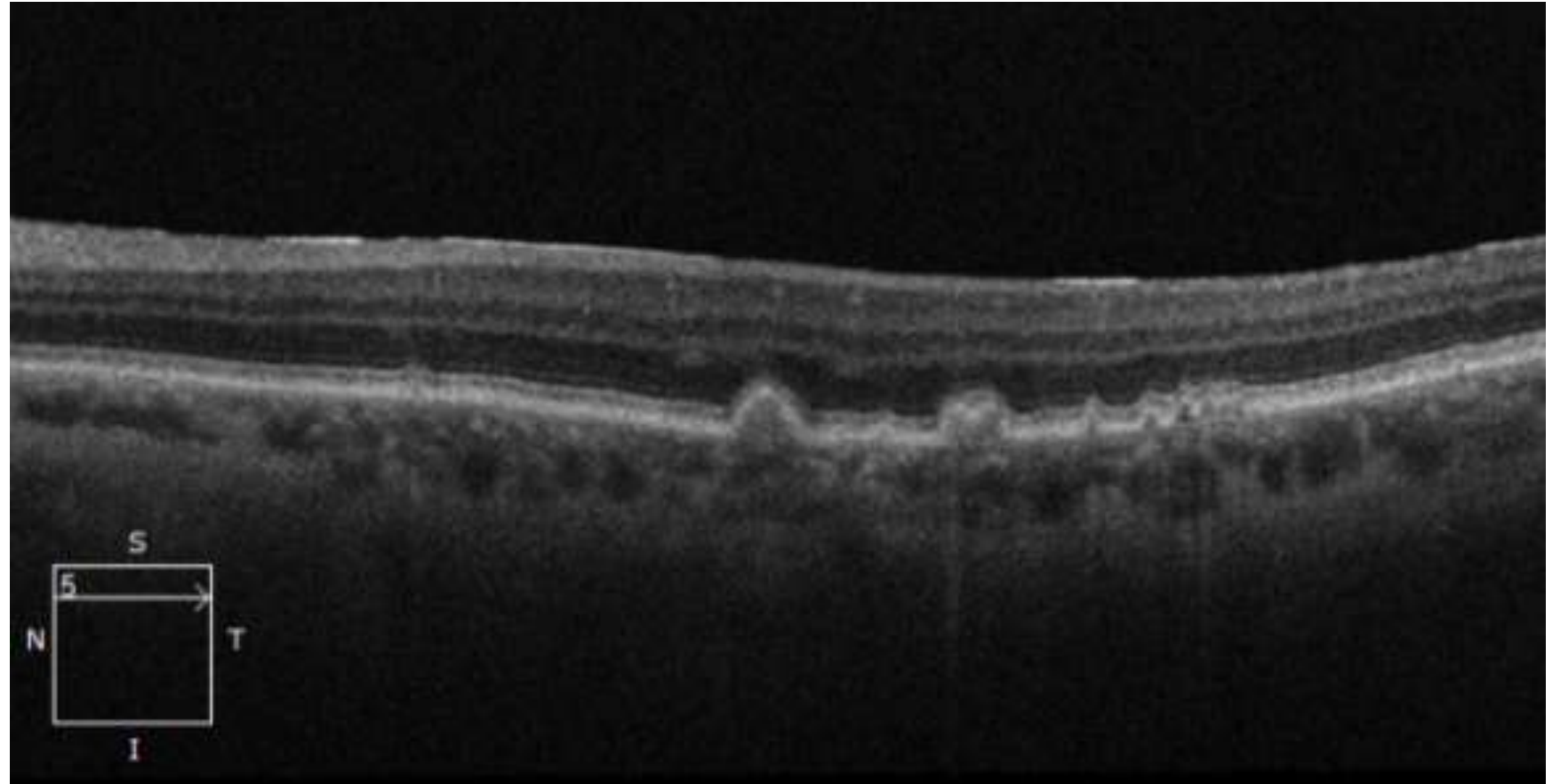
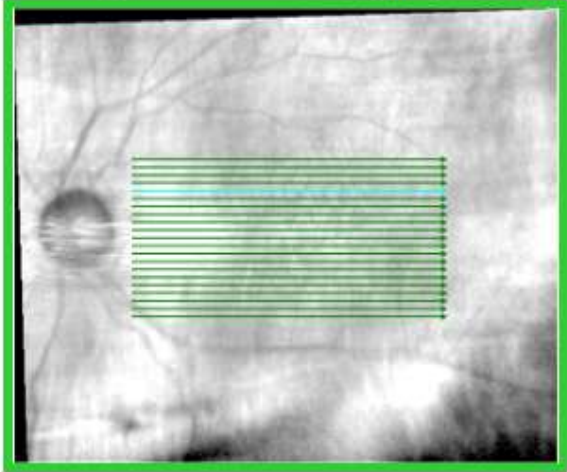
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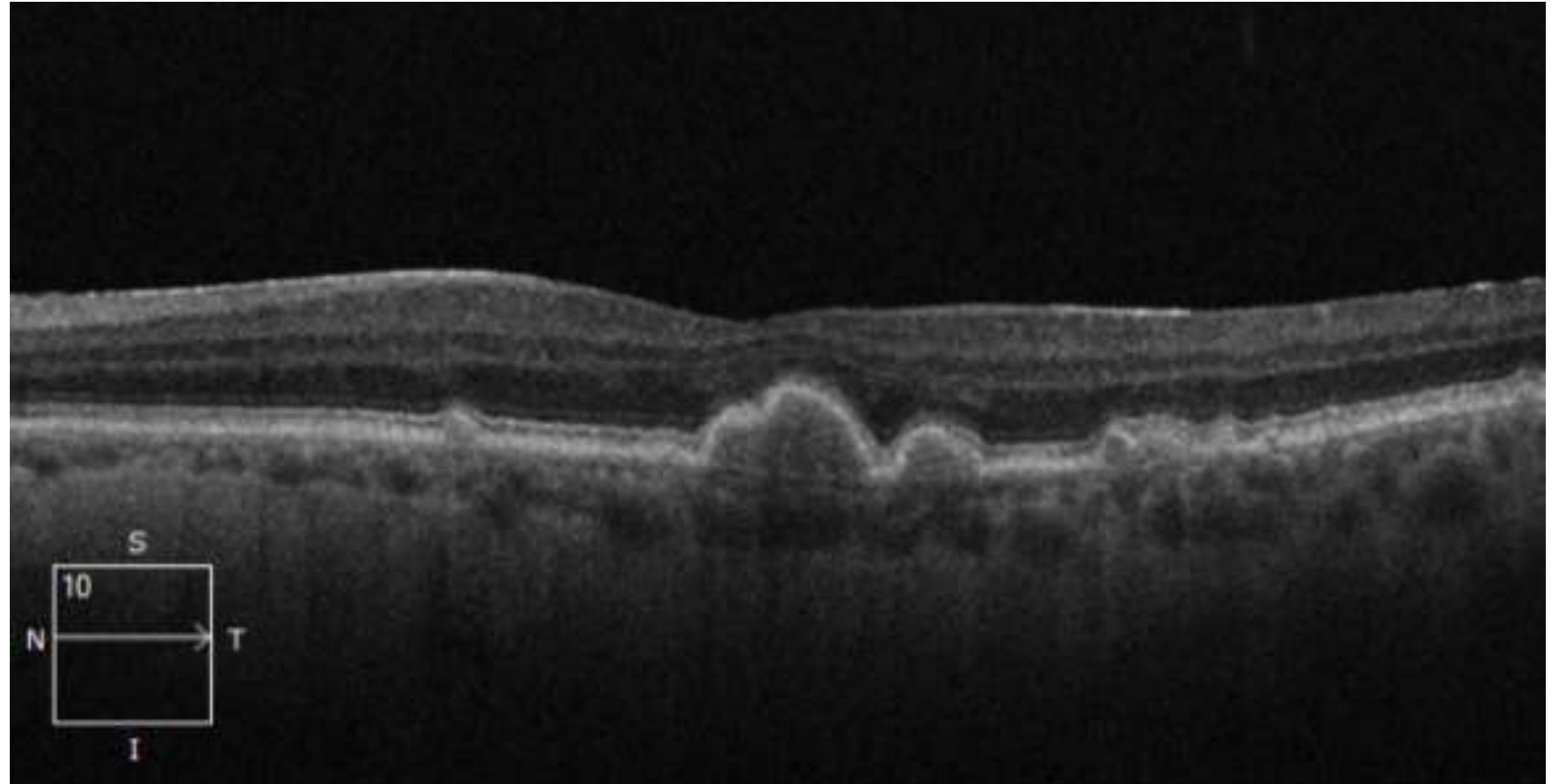
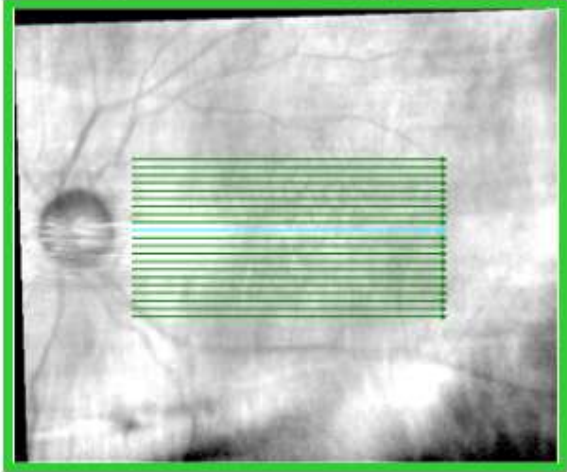
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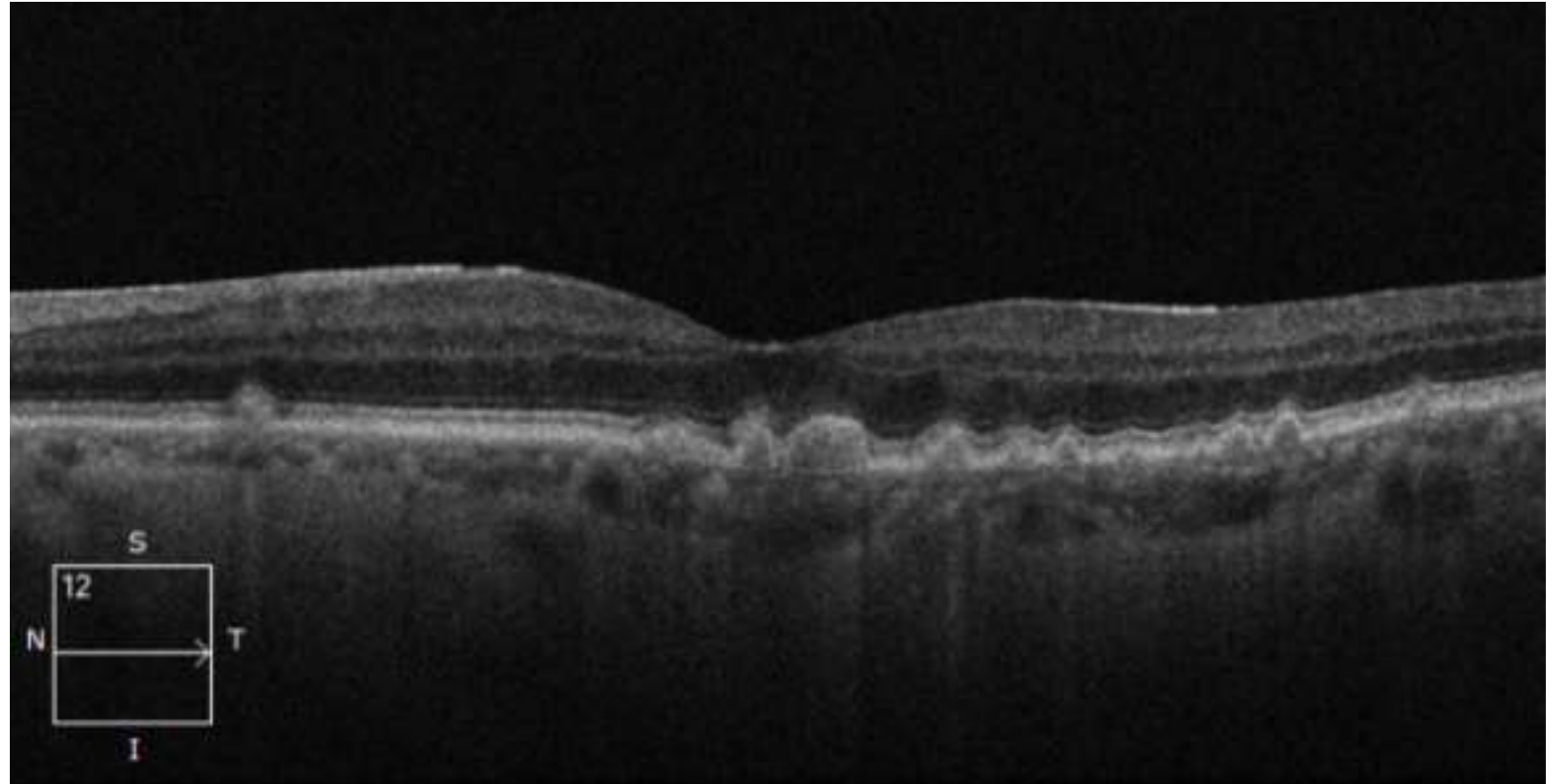
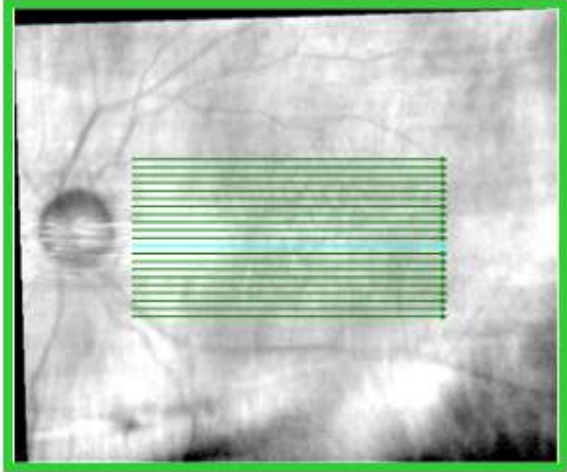
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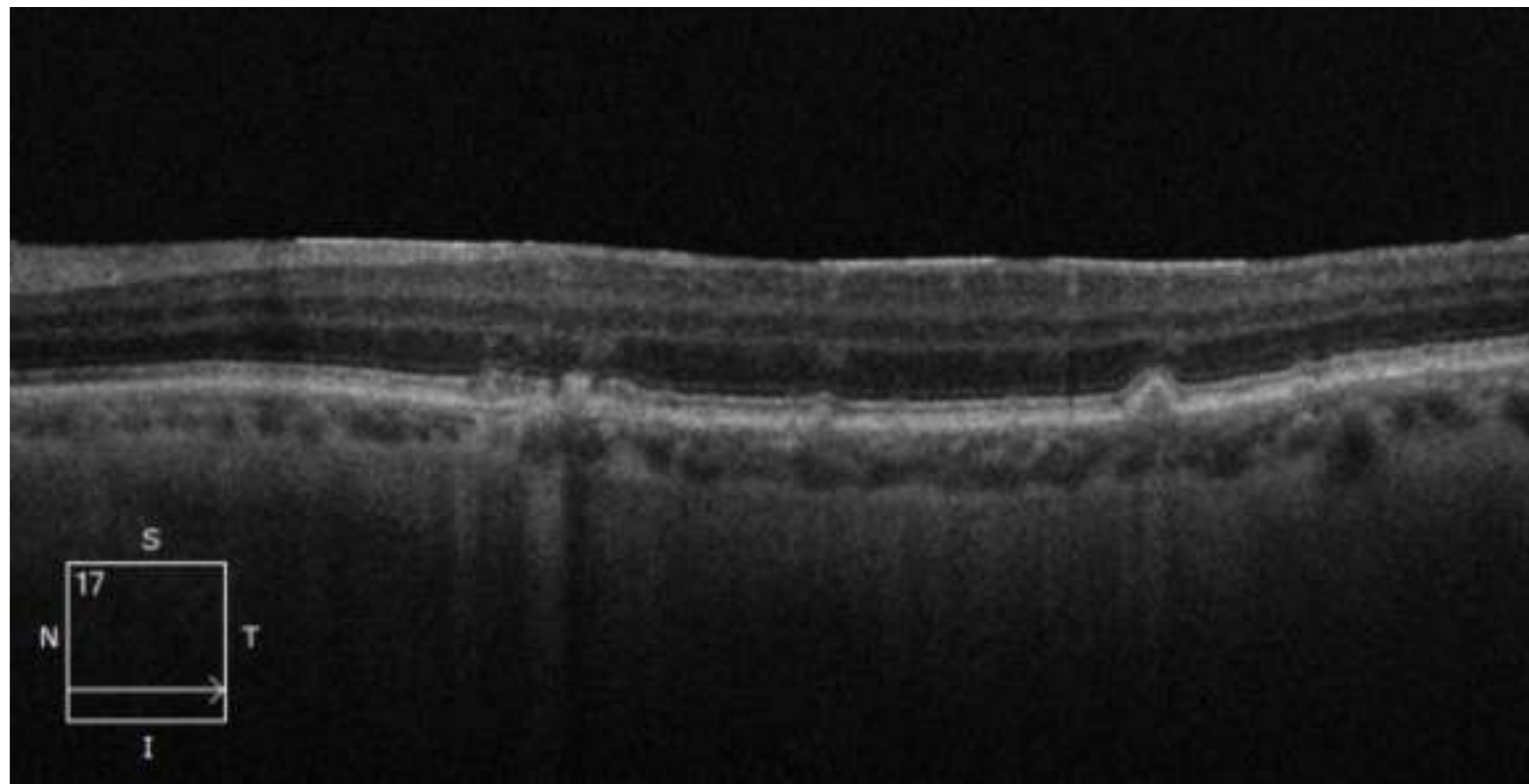
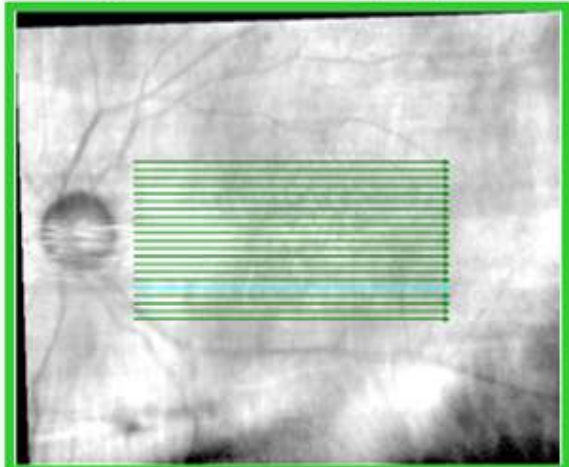
Scan Angle: 0° Spacing: 0.15 mm



Scan Angle: 0° Spacing: 0.15 mm



Scan Angle: 0° Spacing: 0.15 mm

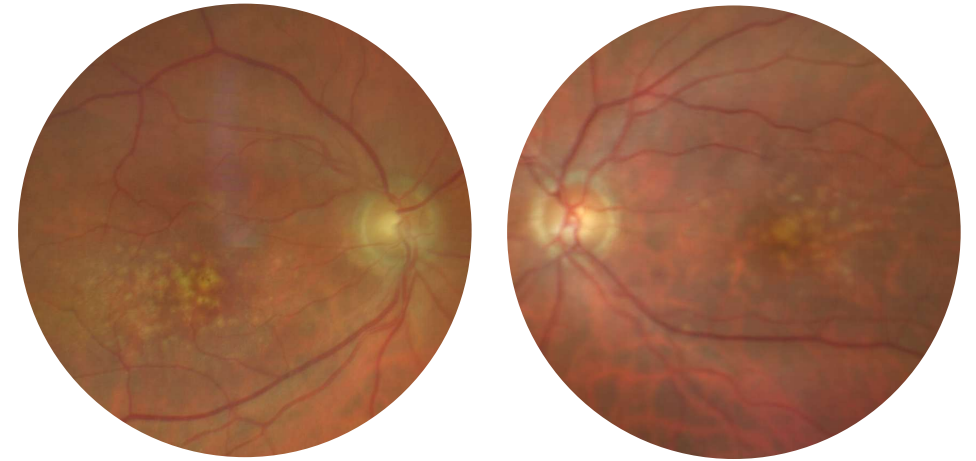




What is your diagnosis?

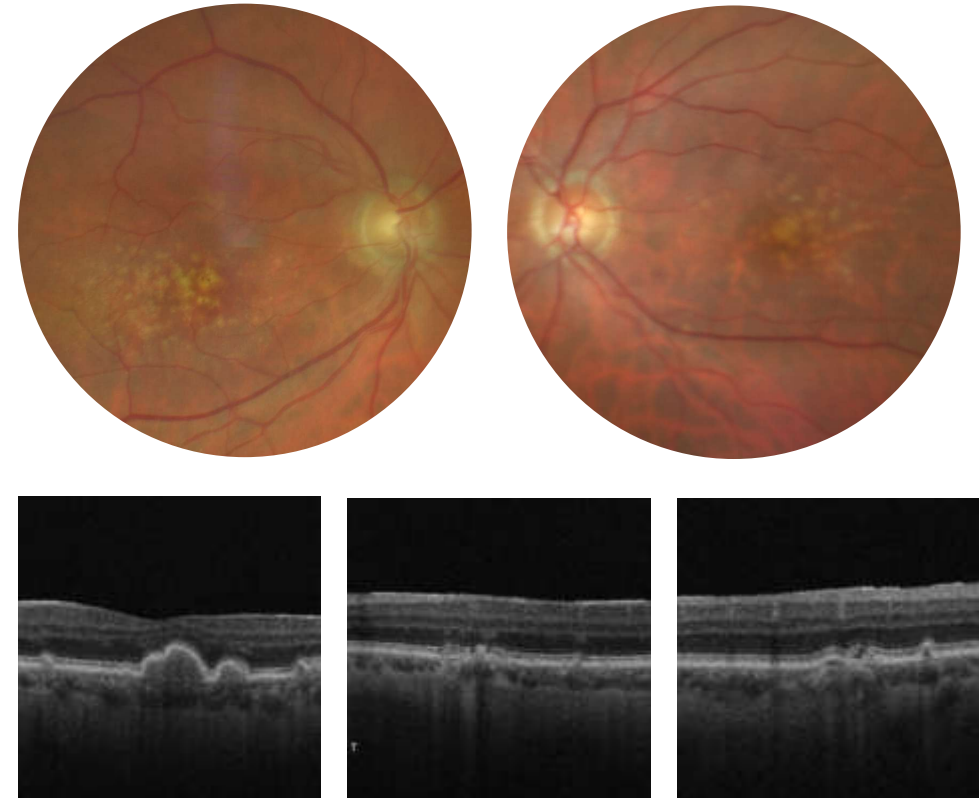
Case analysis (without consideration of biomarkers)

- Dx: intermediate AMD
 - Large drusen and pigmentary abnormalities OU
 - 50% risk of progression in 5 years
- Mgmt: Review in 6-12 months
 - Ongoing AREDS2 type supplementation
 - Amsler grid self-monitoring



Case analysis (with consideration of biomarkers)

- Dx: intermediate AMD
 - Large drusen and pigmentary abnormalities OU
 - 50% risk of progression in 5 years
 - Additional outer retinal band disruptions, hypo-reflective drusen cores, drusenoid PED, possible nascent GA
- Mgmt: Review in 6 months
 - Ongoing AREDS2 type supplementation
 - Amsler grid self-monitoring



Age-related macular degeneration

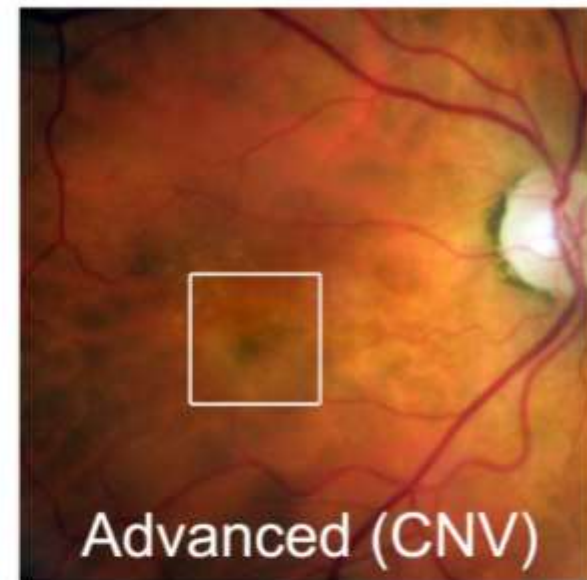
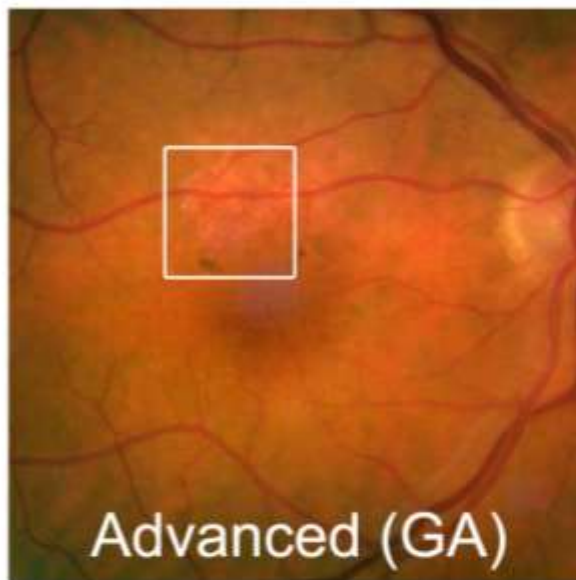
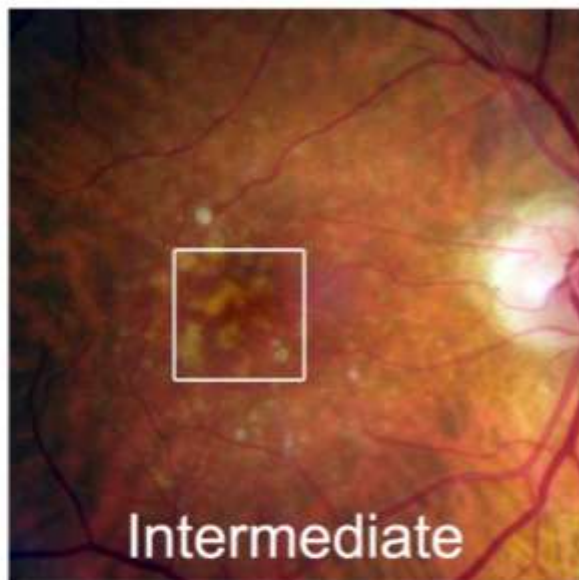
- Terms vary:
 - Okay: Non-exudative, Exudative, Non-neovascular, Neovascular, Atrophic, Druselets
 - Less okay: Quiescent, Pre-clinical, Sub-clinical
 - Not okay: Dry, Wet, Senile, ARM, ARMD
- Complex and multifactorial pathophysiology involving:
 - Senescence/ageing: Changes in BM and the RPE leading to the formation of drusen and lipofuscin, choroidal ischaemia, oxidative stress
 - Local inflammation
 - Angiogenesis



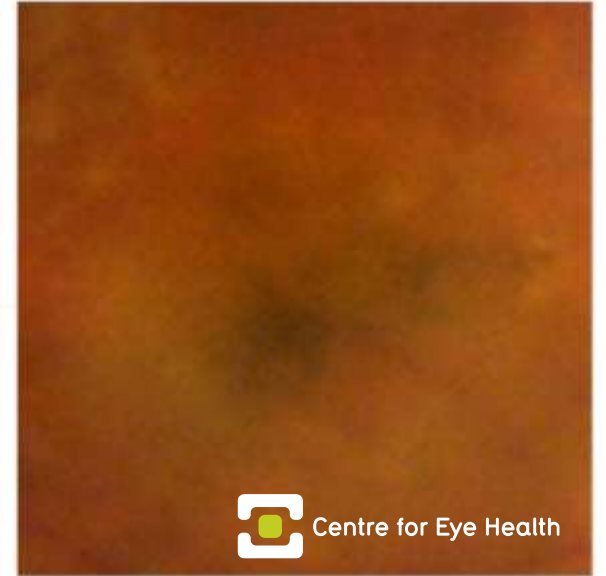
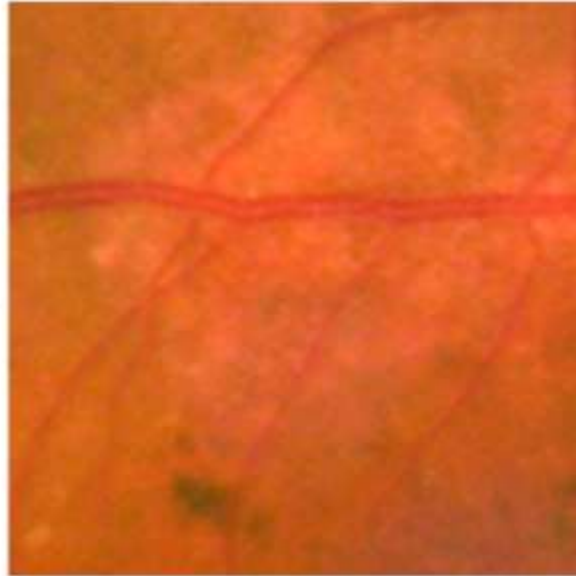
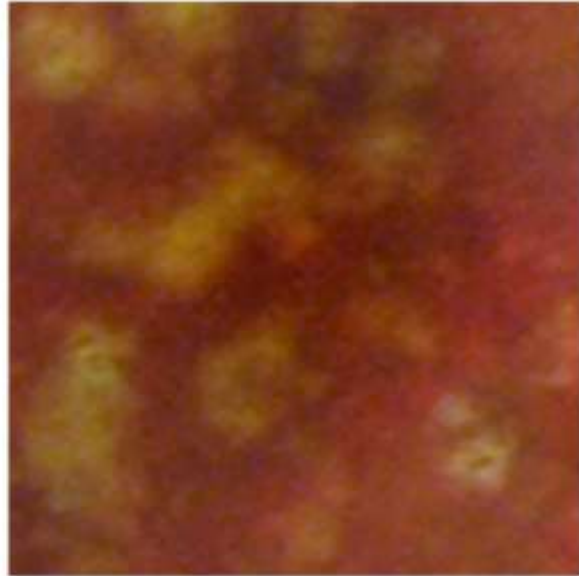
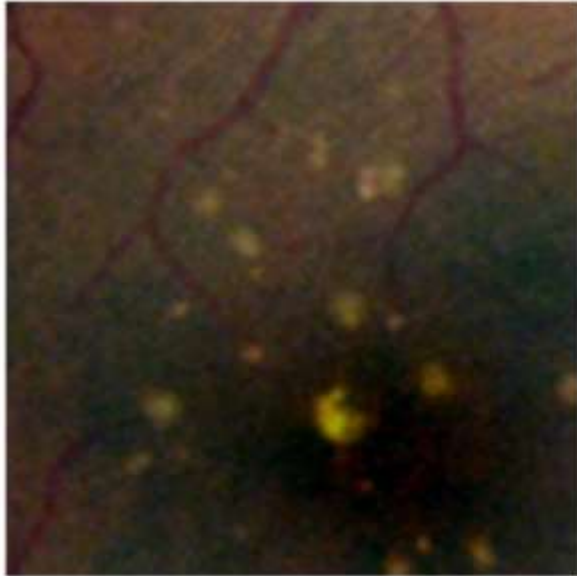
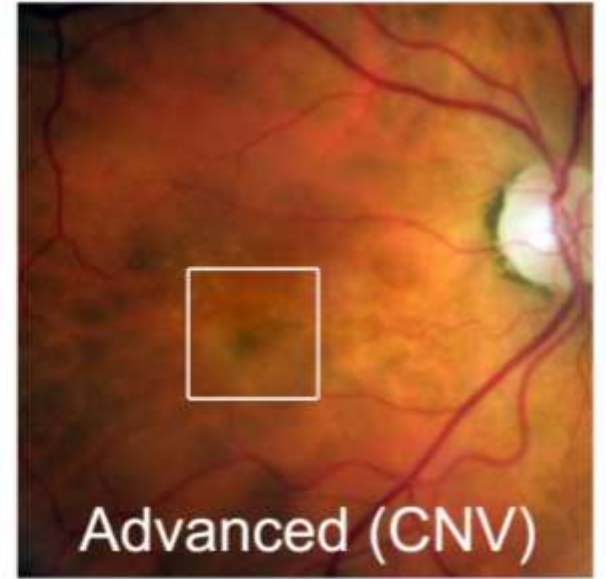
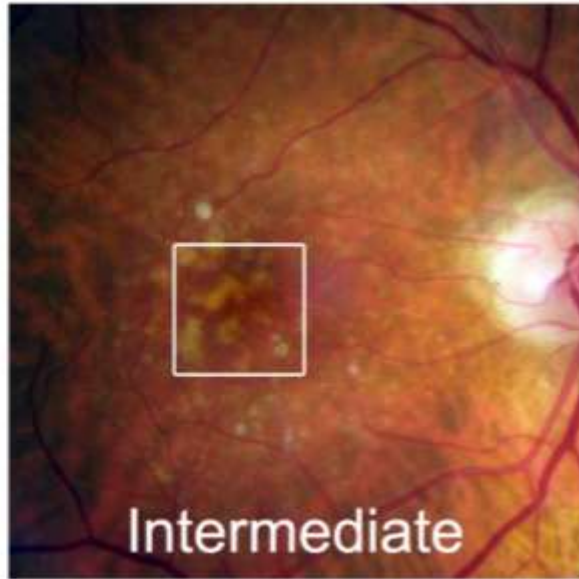
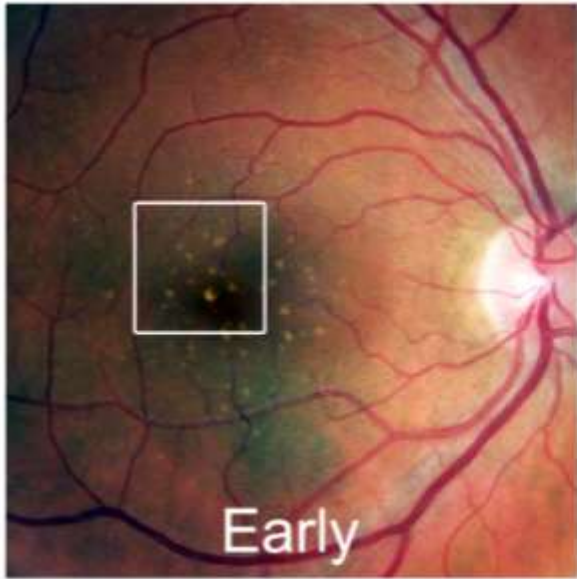
Age-related macular degeneration



- Global prevalence of 8.69% for people aged 45+
- Affects 1 in 7 Australians aged 50+
- Key risk factors: Older age, smoking, genetics (family history and Caucasian ethnicity), cardiovascular risk factors including obesity, HTN, High cholesterol
- Sx differ with disease stage



Wang et al. (2022)

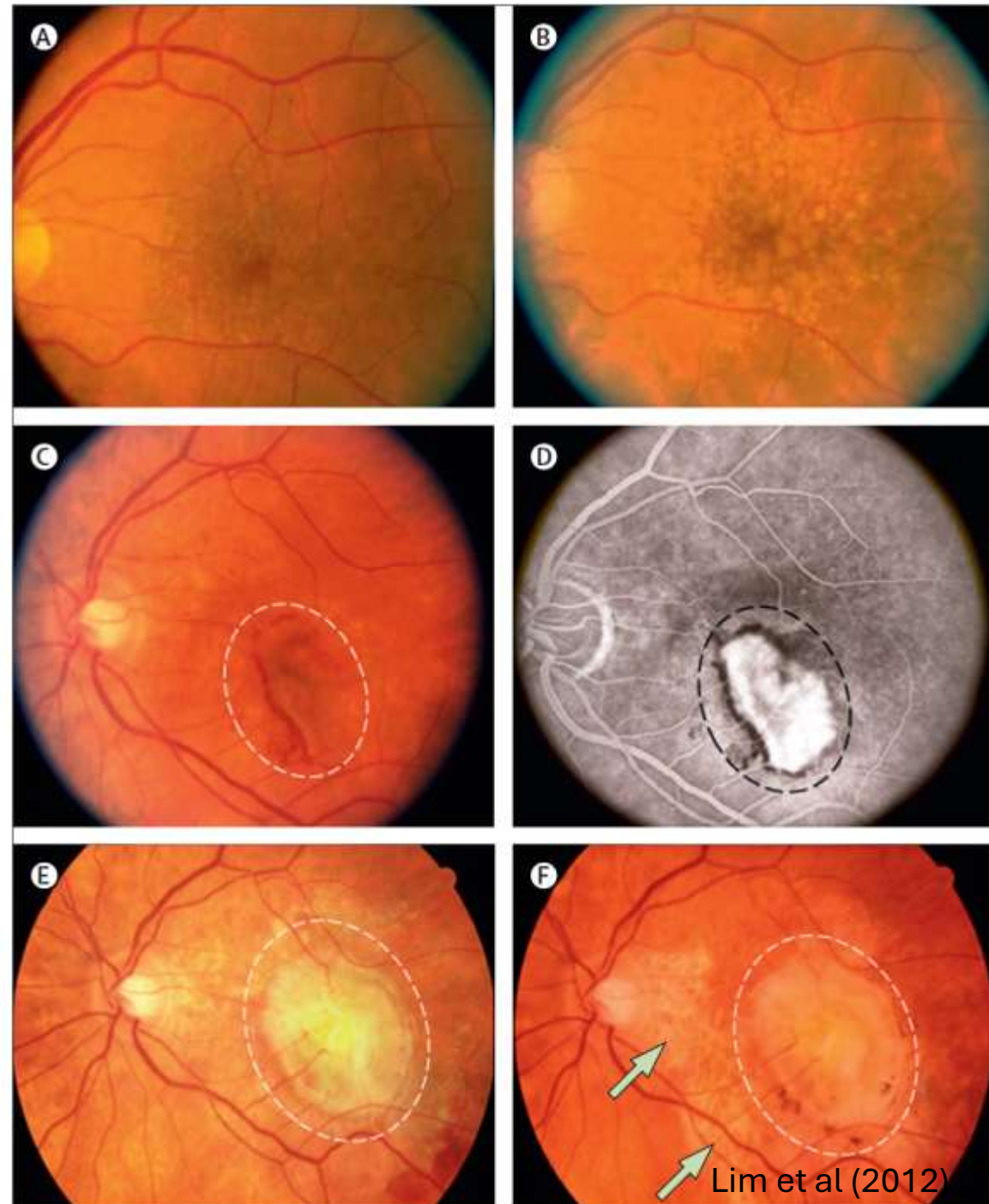


Clinical classification of AMD

- Non-neovascular/Non-exudative AMD (~80%)
 - Characterised by drusen and/or geographic atrophy
 - Slow, progressive and insidious atrophy and loss of the RPE, CC and Ph
 - Vision loss occurs slowly over years
- Neovascular/Exudative AMD (~20%)
 - Vision loss occurs rapidly over months
 - Characterised by any of:
 - Fluid (macular oedema)
 - Lipids (hard exudates, not related to other retinal vascular disease)
 - Blood (sub-retinal haemorrhage)
 - Scarring (fibrosis)
 - RPE detachments (with or without neurosensory retinal detachment)
 - Sub-retinal or sub-RPE neovascular membranes

Management

- nAMD is devastating if untreated
 - 1-3 lines of LogMAR VA lost at 3 months
 - 3-4 lines by 1 year
 - 5 lines by 2 years
- Symptoms: Central vision loss impacting on activities of daily living
- Patients with AMD are at increased risk of:
 - CVD, stroke
 - Reduced quality of life
 - Depression, dementia
 - Falls



Management

**Key question: Which patients
with intermediate AMD are
more likely to progress to
advanced AMD?**



Management and the role of prognostic biomarkers

- The diversity of iAMD has led to “refined phenotyping”
- Core risk factors for advanced AMD described in the AREDS/BIMR and **updated** AREDS simplified severity scale include:
 - Drusen
 - Pigmentary abnormalities
 - Reticular pseudodrusen
- Enabling calculation of risk score between 3-72% over 5 years

**Table 2. Five-Year Rates of Advanced AMD
(in One or Both Eyes for Patients With Both Eyes at Risk)**

Risk Factors	Patients Without Advanced AMD in Either Eye at Baseline*			Patients With Advanced AMD in One Eye at Baseline†		
	No. at Risk	No.	%	No. at Risk	No.	%
0	1466	6	0.4			
1	635	20	3.1			
2	465	55	11.8	149	22	14.8
3	328	85	25.9	178	63	35.4
4	317	150	47.3	273	145	53.1

Abbreviation: AMD, age-related macular degeneration.

*Assign 1 risk factor for each eye with large drusen.

Assign 1 risk factor for each eye with pigment abnormalities.

Assign 1 risk factor if neither eye has large drusen and both eyes have intermediate drusen (Table 1).

†Assign 2 risk factors for the eye that has neovascular AMD.

Assign 1 additional risk factor if the eye at risk has large drusen.

Assign 1 additional risk factor if the eye at risk has pigment abnormalities.

REVIEW

Developing prognostic biomarkers in intermediate age-related macular degeneration: their clinical use in predicting progression

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Age-related macular degeneration is a common, complex and blinding eye disease. When early and intermediate levels of severity are detected in one or both eyes, there is a wide-ranging 0.4 to 53 per cent risk of progression to advanced disease in five years. In order to maximise visual outcomes for their patients, practising eye-care professionals must be able to stratify patients according to their risk of progression, intervene (for example by recommending smoking cessation or nutritional supplements and Amsler grid self-monitoring in intermediate disease) and monitor accordingly. With the aid of ocular imaging, a range of under-recognised yet meaningful risk factors have been identified. The purpose of this review is to assist the eye-care practitioner in stratifying the risk of progression in intermediate age-related macular degeneration using the range of established and emerging precursory signs that herald loss of vision.



OCT Prognostic Biomarkers for Progression to Late Age-related Macular Degeneration

A Systematic Review and Meta-analysis

Matt Trinh, PhD,¹ Rene Cheung, MOptom,^{1,2} Annita Duong, MClinOptom,¹ Lisa Nivison-Smith, PhD,¹ Angelica Ly, PhD¹

Topic: To evaluate which OCT prognostic biomarkers best predict the risk of progression from early/intermediate to late age-related macular degeneration (AMD).

Clinical Relevance: Among > 100 OCT prognostic biomarkers for AMD, it is unclear which are the most relevant for clinicians and researchers to focus on. This review evaluated which OCT biomarkers confer the greatest magnitude of prediction for progression to late AMD.

Methods: Study protocol was registered on PROSPERO (CRD42023400166). PubMed and Embase were searched from inception to March 2, 2023, and eligible studies assessed following the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach. The primary outcome was any quantified risk of progression from treatment-naive early/intermediate AMD to late AMD, including hazard ratios (HRs), odds ratios (ORs), and standardized mean differences (at baseline, between eyes with versus without progression), subgrouped by each OCT biomarker. Further meta-analyses were subgrouped by progression to geographic atrophy or neovascularization.

Results: A total of 114 quantified OCT prognostic biomarkers were identified. With high GRADE certainty of evidence, the greatest magnitudes of prediction to late AMD belonged to: external limiting membrane abnormality (OR, 15.42 [7.63, 31.17]), ellipsoid zone abnormality (OR, 10.8 [4.58, 25.46]), interdigitation zone abnormality (OR, 7.68 [2.57, 23]), concurrent large drusen and reticular pseudodrusen (HR, 6.73 [1.35, 33.65]), hyporeflective drusen cores (HR, 2.48 [1.8, 3.4]; OR 1.85 [1.29, 2.66]), intraretinal hyperreflective foci (IHRF; HR, 2.16 [0.92, 5.07]; OR 5.08 [3.26, 7.92]), and large drusen (HR, 2.01 [1.35, 2.99]); OR, 1.98 [1.27, 3.08]). There was greater risk of geographic atrophy for IHRF and hyporeflective drusen cores ($P < 0.05$), and neovascularization for ellipsoid zone abnormality ($P < 0.05$). Other OCT biomarkers such as drusenoid pigment epithelium detachment, shallow irregular retinal pigment epithelium elevations, and nascent geographic atrophy exhibited large magnitudes of risk but required further studies for validation.

Conclusion: This review synthesizes the 6 most relevant OCT prognostic biomarkers for AMD with greater predictive ability than large drusen alone, for clinicians and researchers to focus on. Further study is required to validate other biomarkers with less than high certainty of evidence, and assess how the copresence of biomarkers may affect risks.

Financial Disclosure(s): The author(s) have no proprietary or commercial interest in any materials discussed in this article. *Ophthalmology Retina* 2024;8:553-565 © 2023 by the American Academy of Ophthalmology

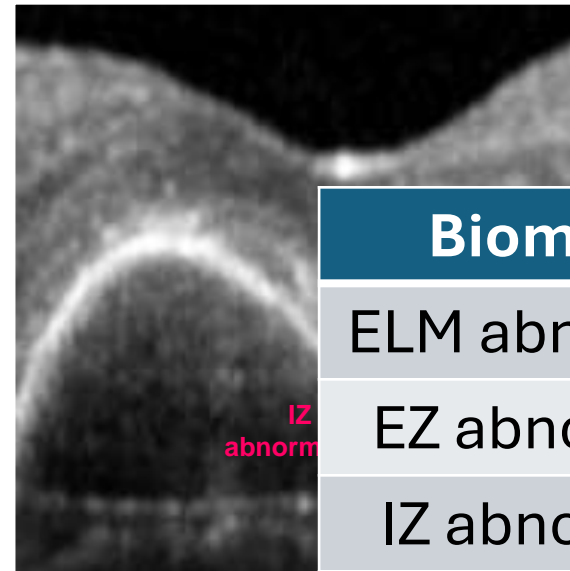
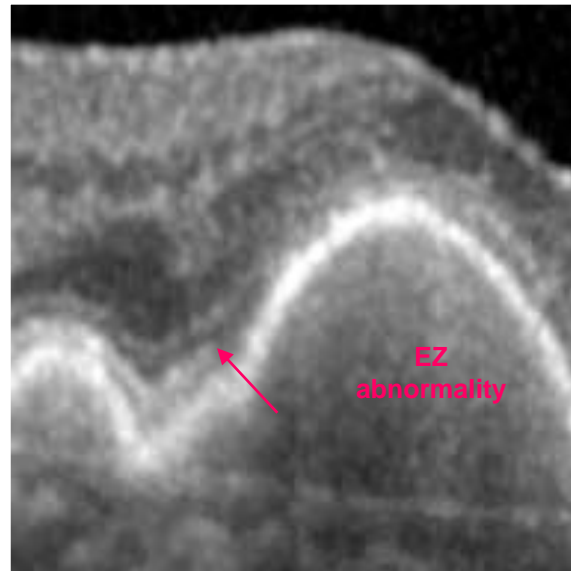
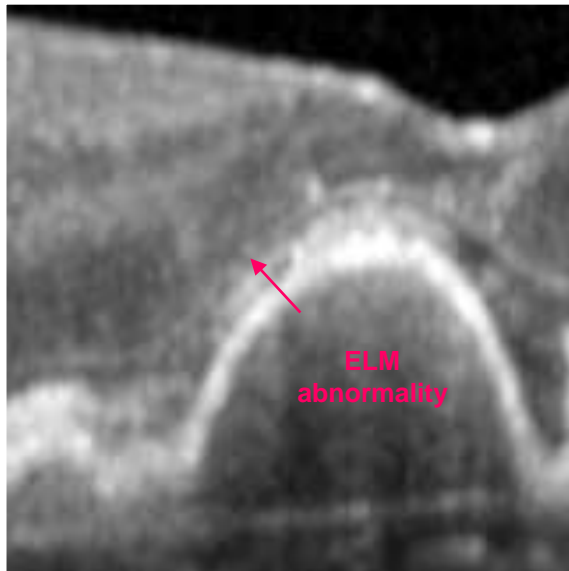
Drusen regression



- Occurs in 20-50% of AMD cases over 2 years
 - More likely in eyes with greater baseline drusen area/volume
- Carries a strong association with advanced AMD (up to 82%)
 - All cases of GA/CNV are preceded by drusen regression

Abnormality of the hyper-reflective outer retinal bands

- Carry a 7.7 to 15.4x odds ratio (increased risk of late AMD)
- EZ can also be useful to assess treatment efficacy

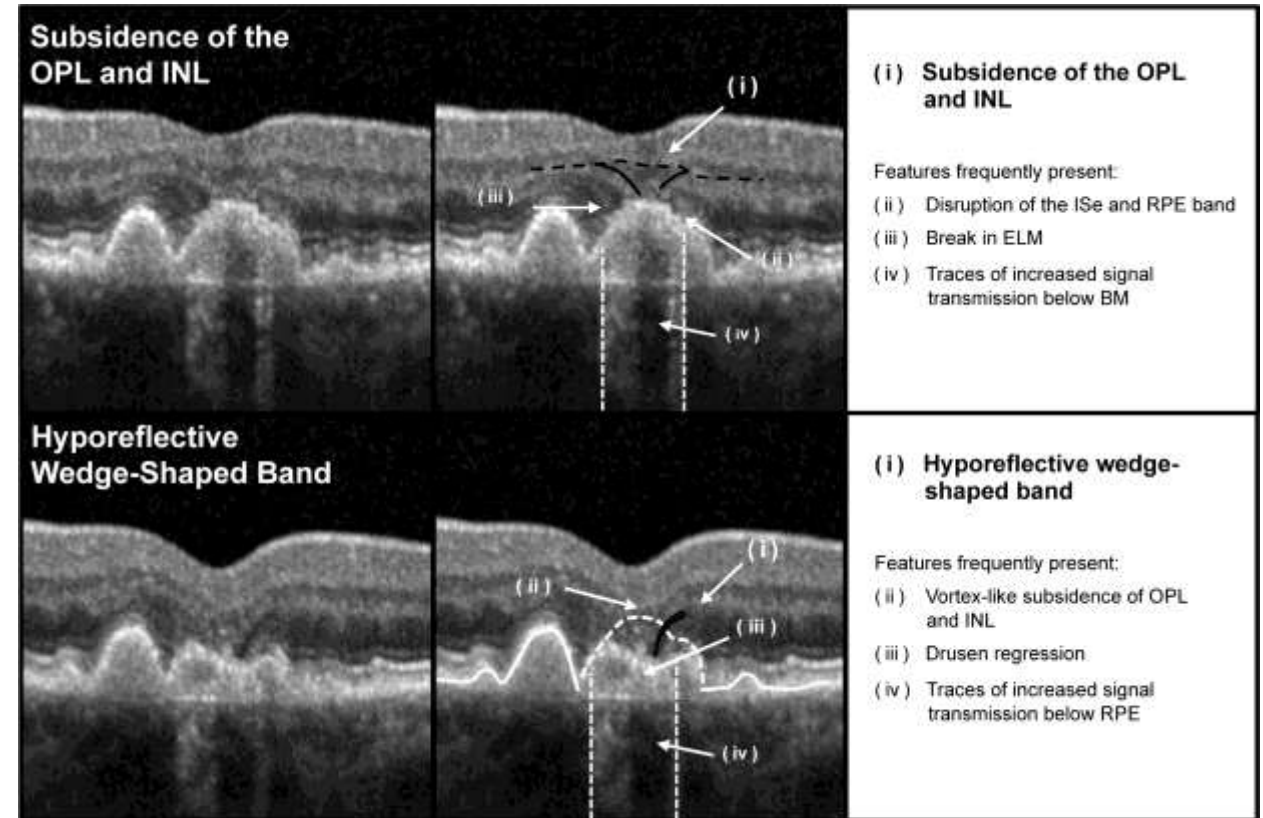


Images courtesy of Dr Matt Trinh

Biomarker	Effect size (s)
ELM abnormality	15.42
EZ abnormality	10.8
IZ abnormality	7.68
Large drusen	1.98

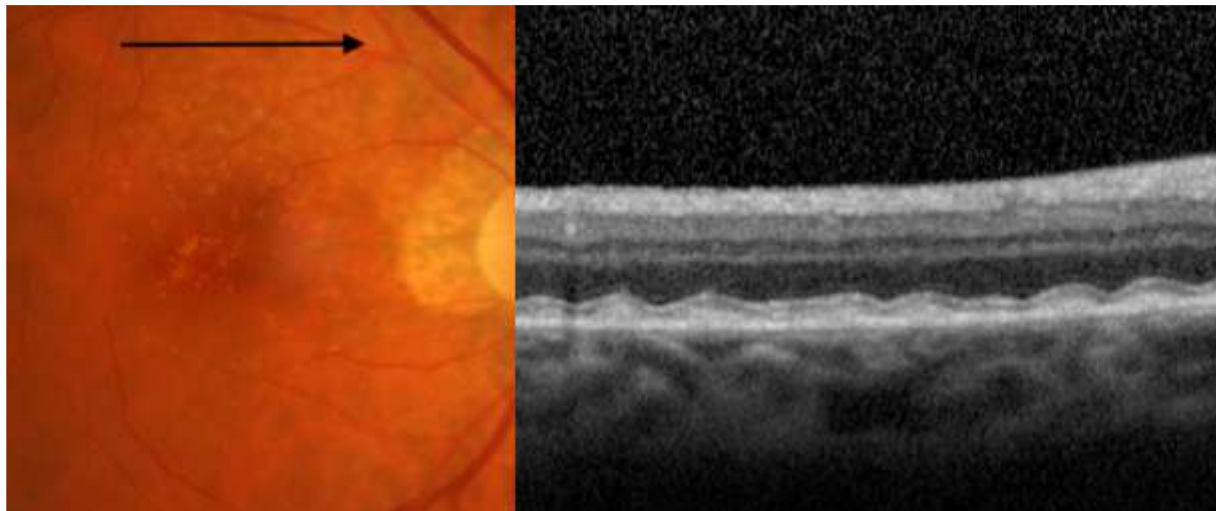
Nascent geographic atrophy

- Presence of either
 - Seen in established GA
 - Also portend GA development
- High-risk factor for GA development



Reticular pseudodrusen

- Regular, yellow-white, interlacing deposits usually in the superior macula
- Appear as subretinal drusenoid deposits using OCT
- Approximately doubles the risk of advanced AMD in 5 years



Risk factors	5-year rate of advanced AMD	
	Without RPD	With RPD
0	0.5%	3%
1	4%	8%
2	12%	30%
3	25%	60%
4	50%	70%

Hypo-reflective drusen cores

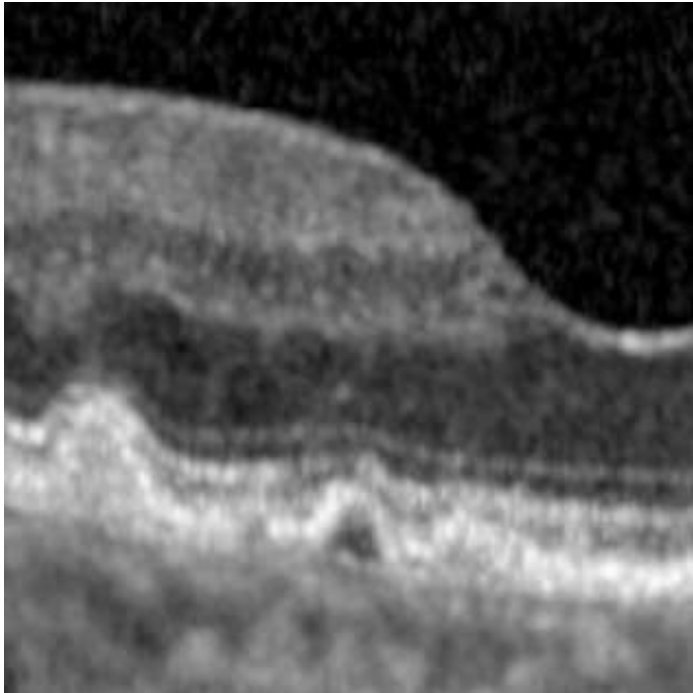
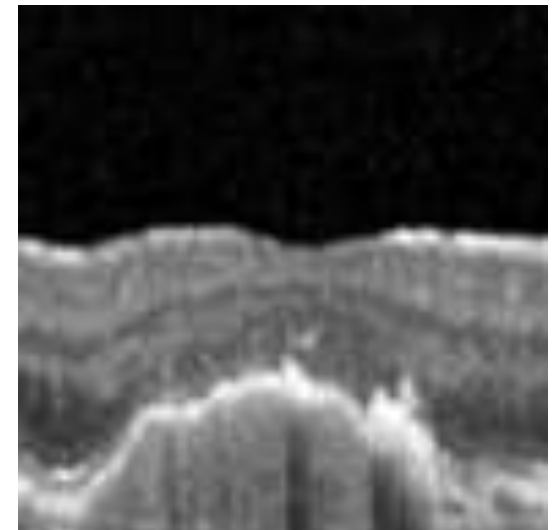
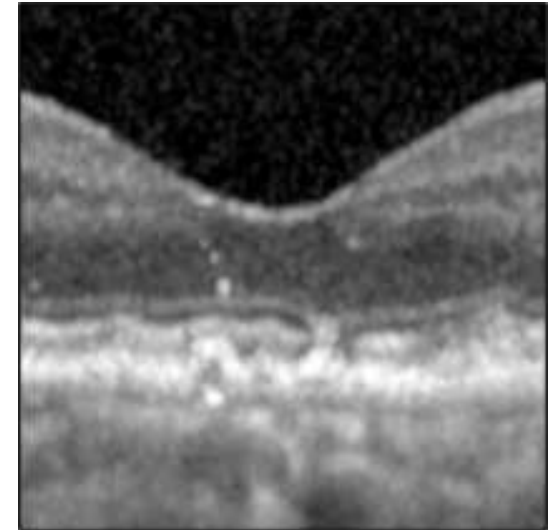


Image courtesy of Dr Matt Trinh

- Represent drusen ‘softening’/internal atrophy and impending collapse

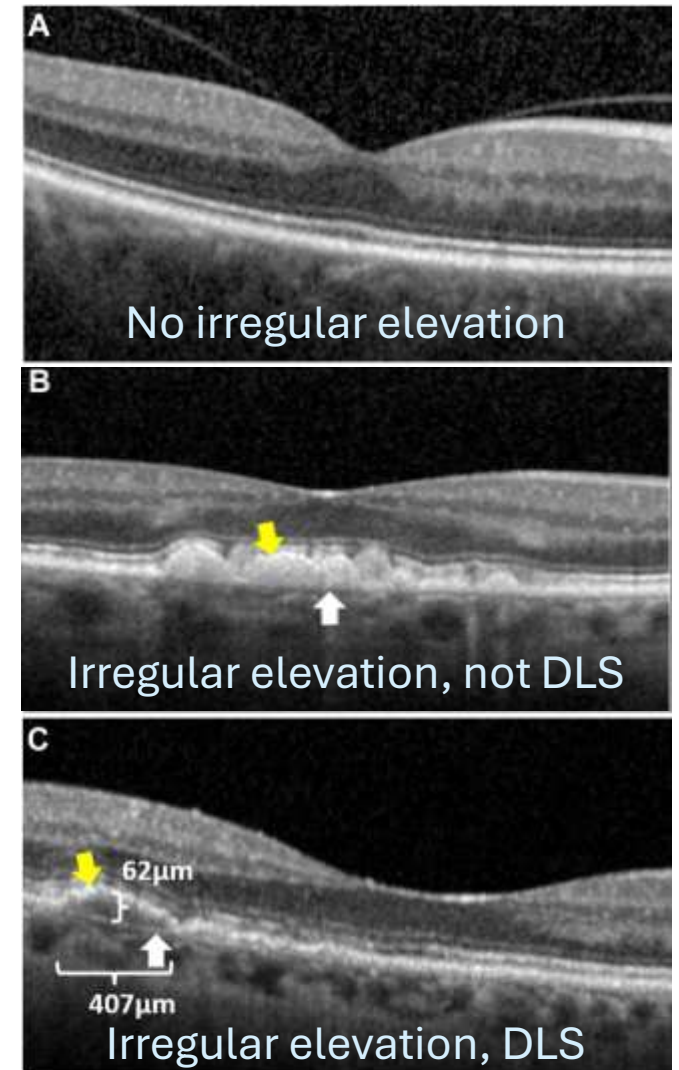
Hyper-reflective foci

- Typically correspond with pigmentary abnormalities/RPE migration
- Can also correspond with lipid-laden macrophages, microglial cells, protein or lipid material



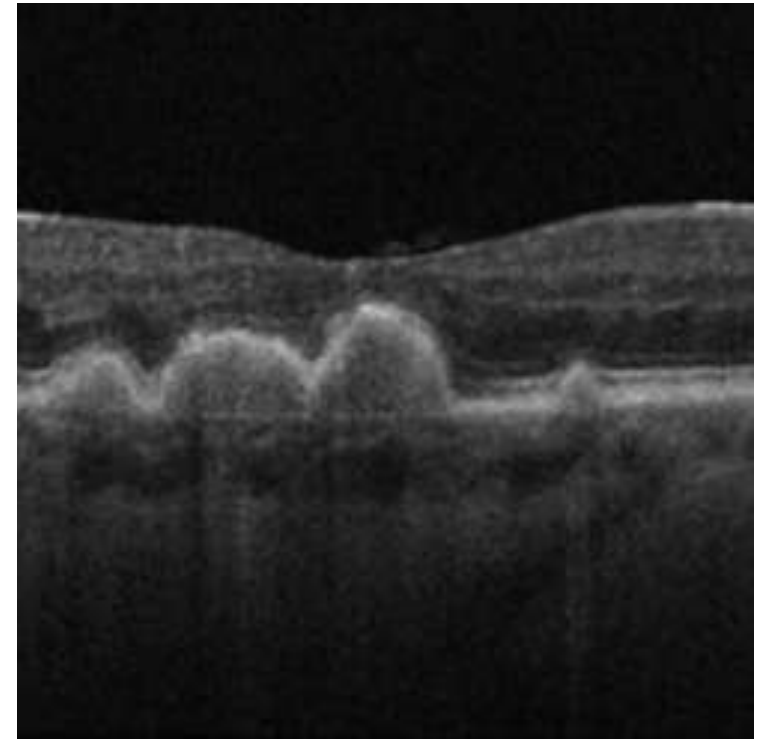
Double layer sign

- Indication for OCTA and/or FFA
- May signify dormant nonexudative MNV in AMD or other macular disease e.g., PCV
- Low-lying (irregular) elevation of the RPE defined by the presence of a highly reflective RPE layer and a further highly reflective layer composed of BM on its outer aspect
- Must show **internal heterogenous reflectivity**



Drusenoid PED

- Large or confluent drusen $\geq 350\mu\text{m}$ narrowest diameter





What is the **AREDS/BIMR** size criterion for large drusen?

Management of early AMD

- Aimed at reducing the risk of progression
- Modify nutrient intake
 - Antioxidant rich foods – carotenoids (lutein, zeaxanthin or beta-carotene), vitamin C and vitamin E
 - Some evidence for omega-3 (found in Ph outer segment membranes)
- Modify other lifestyle factors
 - Cigarette smoking
 - Obesity, cardiovascular health (exercise)
 - Some weak evidence regarding sunlight exposure

Management of intermediate AMD



Management of late AMD

- Early detection is vital
- New treatments for geographic atrophy are here!
- Anti-VEGF for MNV
- Low vision assessment and rehabilitation





Which of the following carries the highest risk of progression to advanced AMD? According to a recent meta-analysis by Trinh et al.

Key points for case study 2: Once you see it, you can't unsee it

- Prognostic biomarkers describe signs in addition to the AREDS severity scale that can be useful for predicting which patients will progress to advanced AMD
- Integrity of the outer retinal bands in AMD carry a larger risk of progression than large drusen

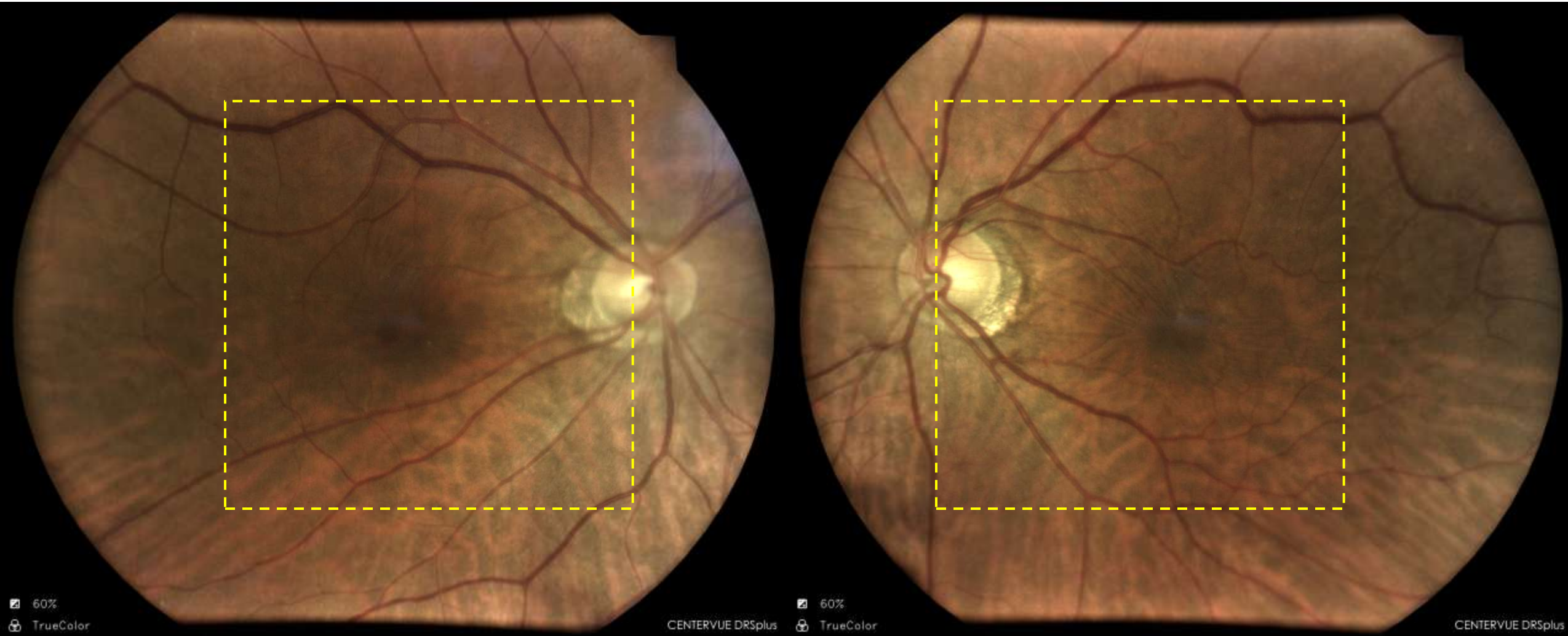
Do you see what I see?

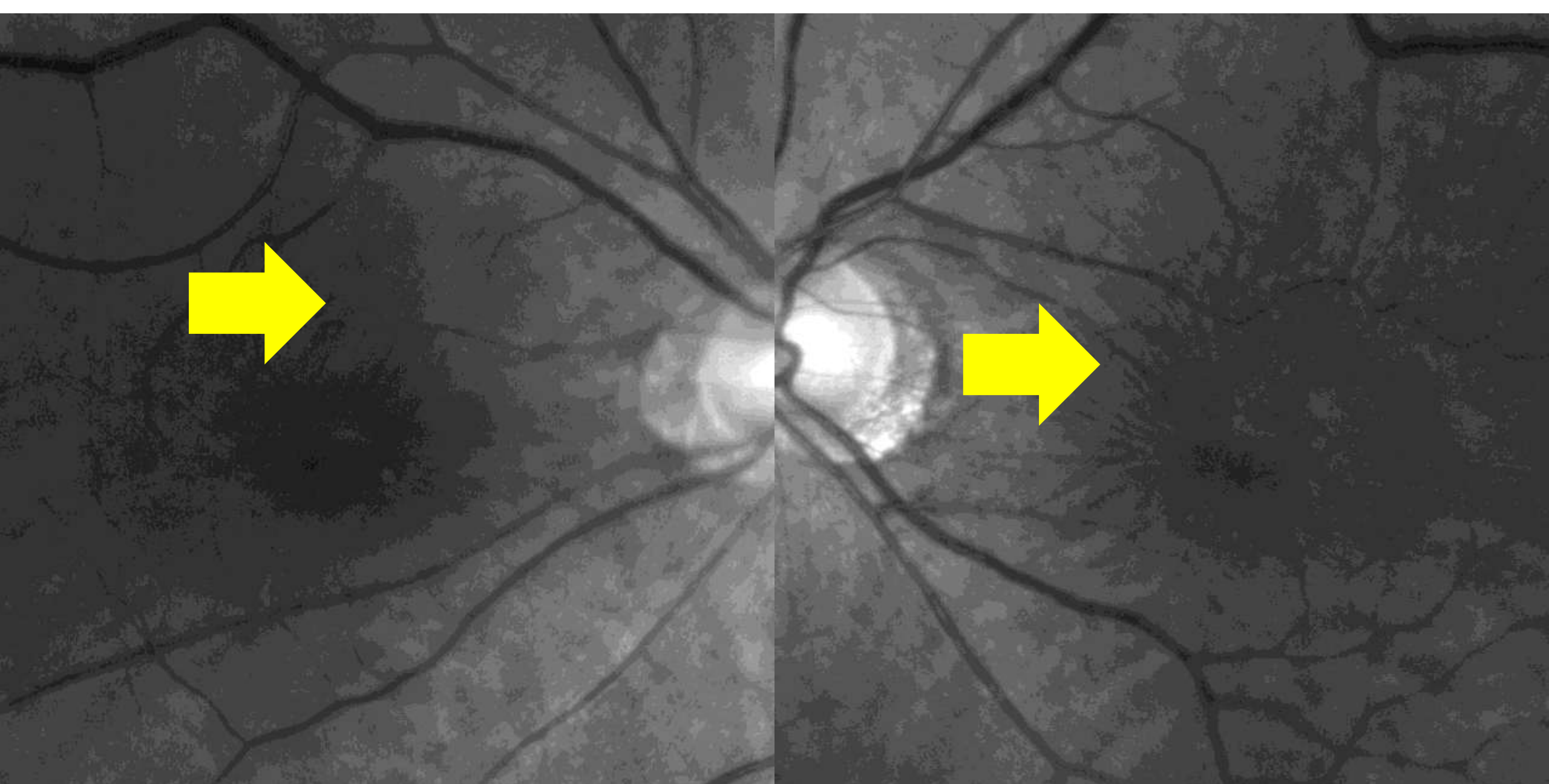
Predictive biomarkers in epiretinal membrane

Case study

- Asymptomatic 64yo female
- Presented for a routine checkup, known macular disease OU
- No flashes, floaters or metamorphopsia
- PMHx: Sjögren's syndrome, methotrexate for rheumatoid arthritis

	OD	OS
Refraction	-3.25/-0.50x85	-2.50/-1.00x104
BCVA	6/7.6-	6/9.5-2
Amsler grid	Unremarkable	Unremarkable



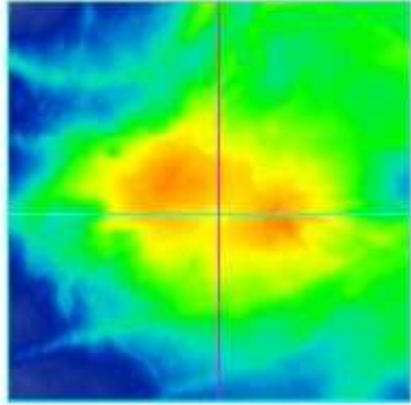


Images courtesy of the SOVS Optometry Clinic © 2025 University of New South Wales. All rights reserved.

Macula Thickness OU: Macular Cube 512x128

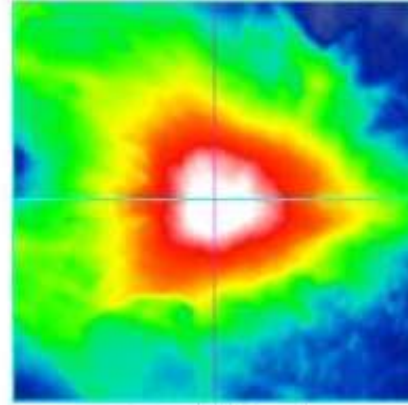
OD ● OS

OD ILM-RPE Thickness Map

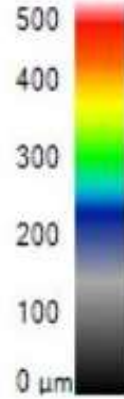


Fovea: 269, 69

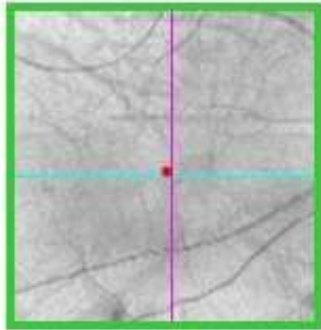
OS ILM-RPE Thickness Map



Fovea: Not found



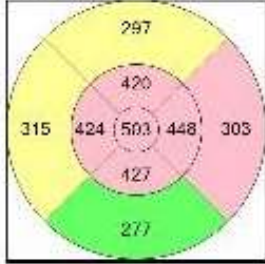
OD OCT Fundus



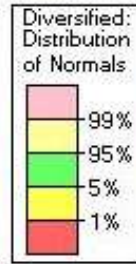
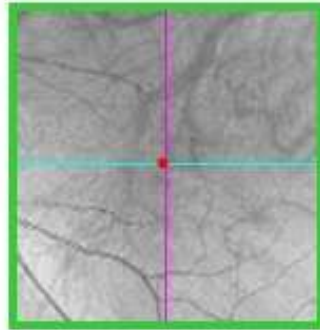
OD ILM-RPE Thickness



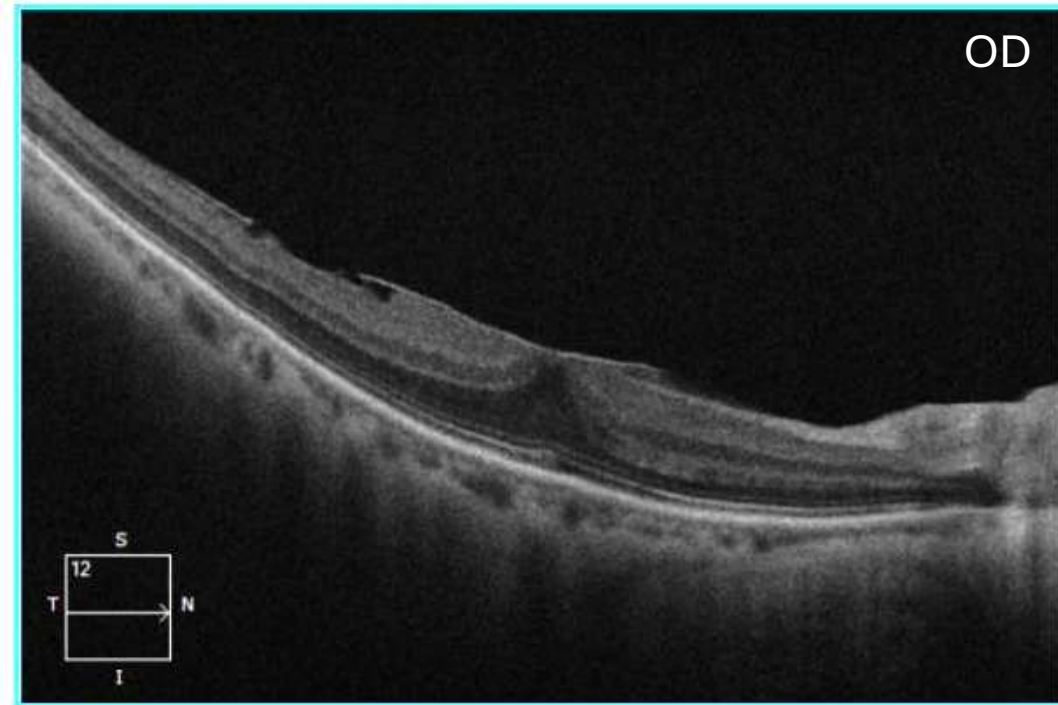
OS ILM-RPE Thickness



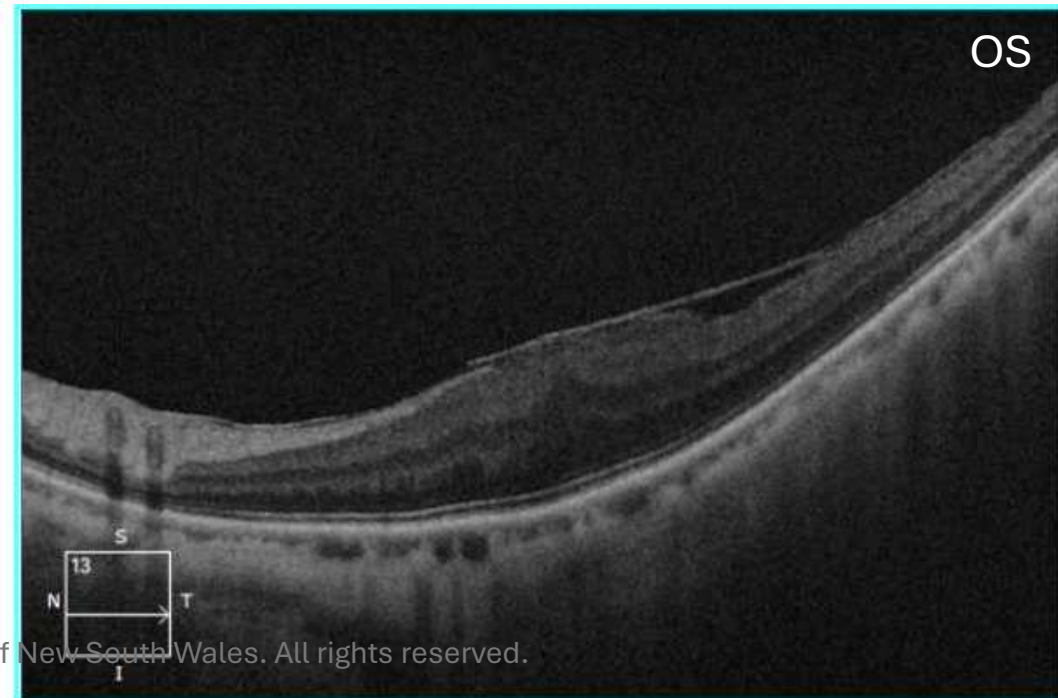
OS OCT Fundus



ILM - RPE	OD	OS
Thickness Central Subfield (µm)	377	503
Volume Cube (mm³)	10.5	11.4
Thickness Avg Cube (µm)	291	316



OD



OS



What biomarker is present in the left eye OCT image?

Macula Thickness OU: Macular Cube 512x128

OD ● OS

OD ILM-RPE Thickness Map

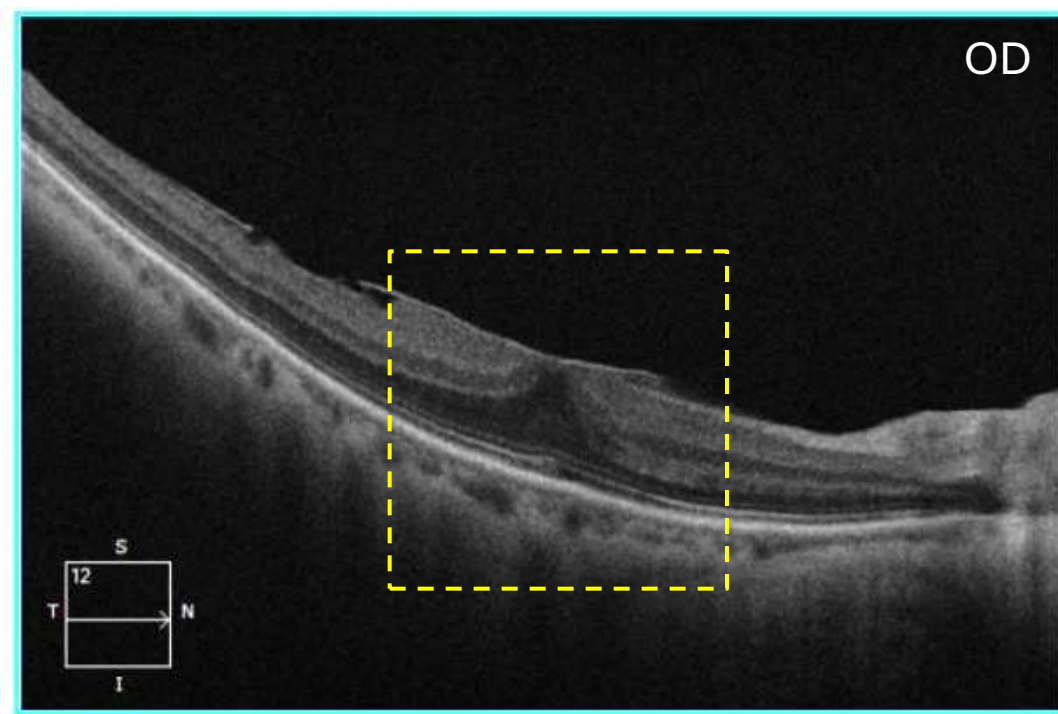
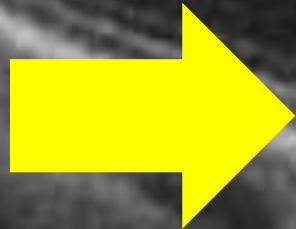
OS ILM-RPE Thickness Map

500

Fovea:

OD OCT Fundus

Fundus



OD



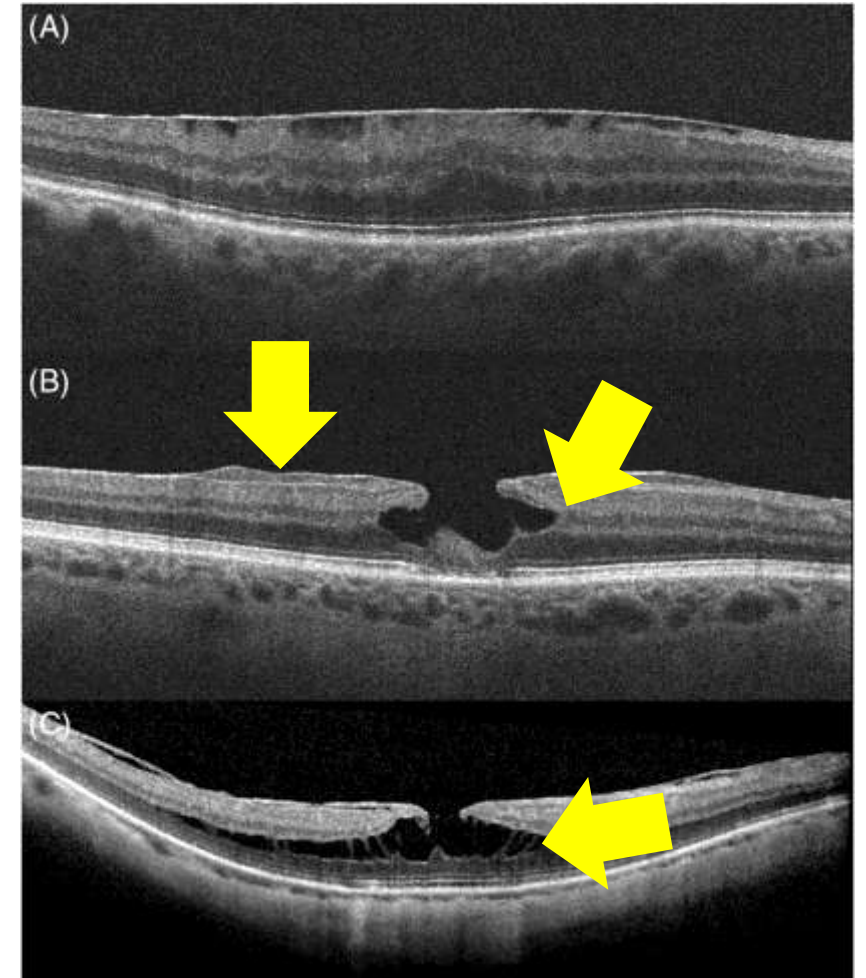
OS



What is your diagnosis?

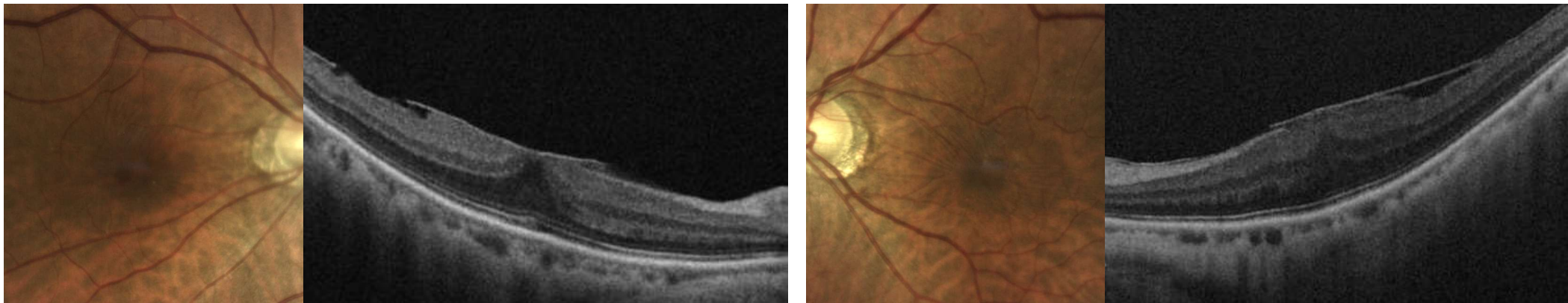
Top three differential diagnoses

- Epiretinal proliferation: isorefective
- Lamellar macular hole: undermined edges
- Foveoschisis: intraretinal separation



Case analysis (without consideration of biomarkers)

- Dx: Intermediate epiretinal membrane with PVD OU
 - Distortion of the inner retina – retinal folds, surface wrinkling
- Mgmt: Patient is asymptomatic, review 6-12months with DFE+OCT
- Interim Amsler grid self-monitoring and Px education

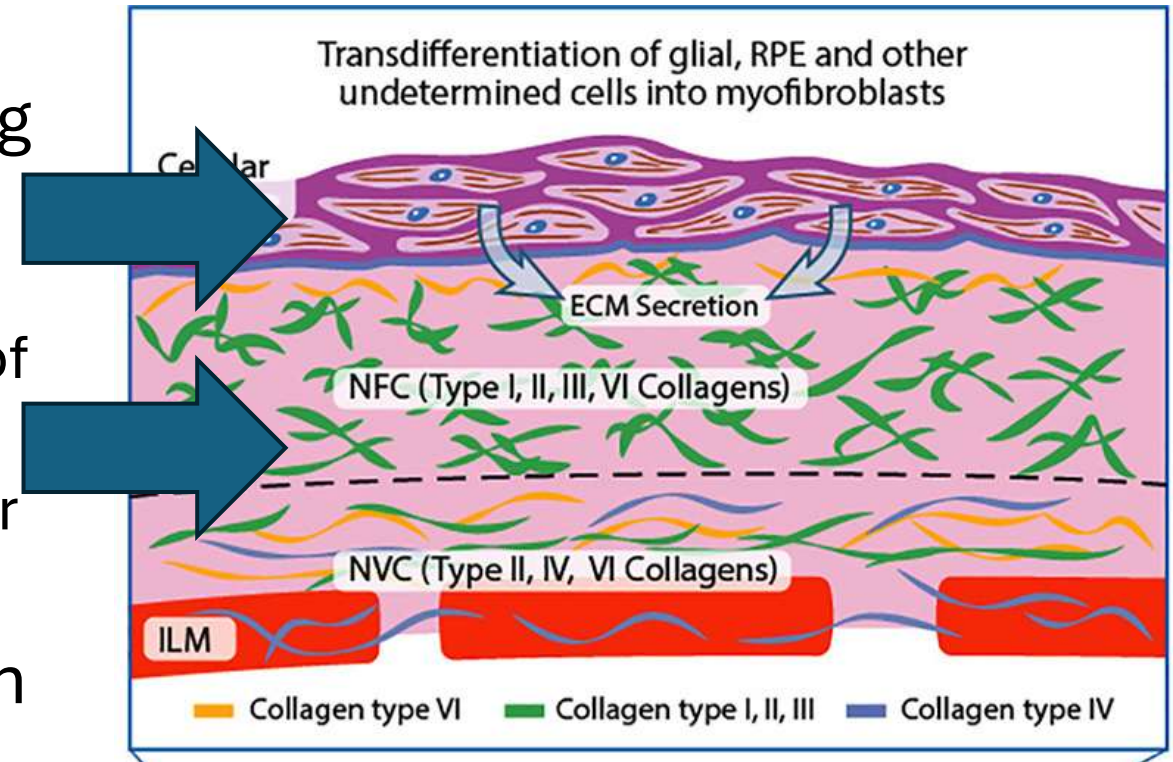


Case analysis (with consideration of biomarkers)

- Intermediate epiretinal membrane
 - Partially adhered with PVD OU
 - Distortion of the inner retina – retinal folds, surface wrinkling
 - Cotton ball sign OD, EIFL OS
- Original mgmt: Patient is asymptomatic, review 6-12months
- **Revised mgmt: Refer to a vitreoretinal specialist for opinion**

Epiretinal membrane

- Composed of two layers overlying the ILM
 - Outermost layer of non-cellular ECM proteins containing bundles of extracellular fibrils
 - Overlying inner single or multi-layer cellular component
- ERM progression = accumulation of contraction of cells and ECM



Epiretinal membrane

- Prevalence of 9.1%
- Major risk factor is age
- Primary, idiopathic or secondary
- Bilateral in 19.5% - 31%
- May be asymptomatic
- Symptoms depend on location, duration, severity and type: reduced VA, blurred vision, metamorphopsia, loss of stereopsis, aniseikonia, binocular interference

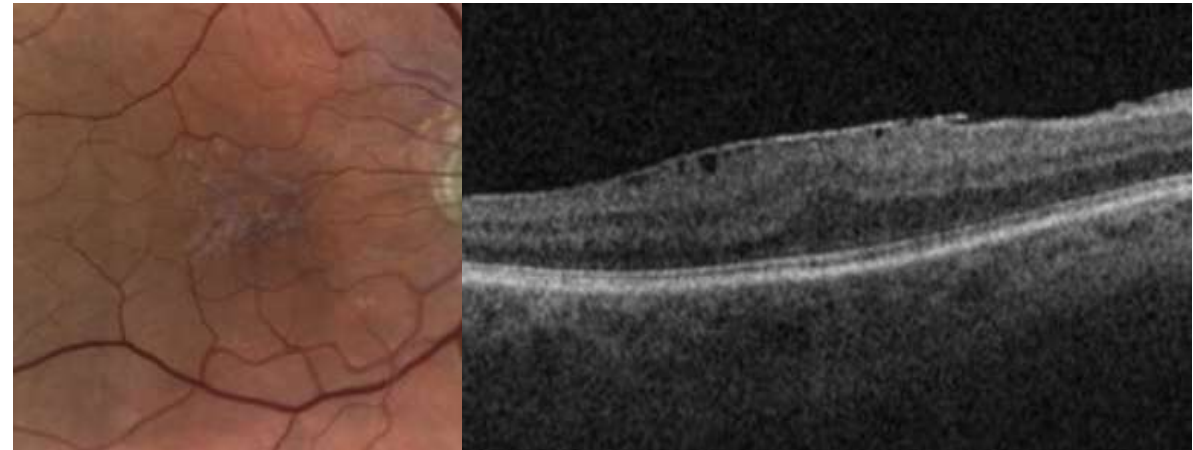
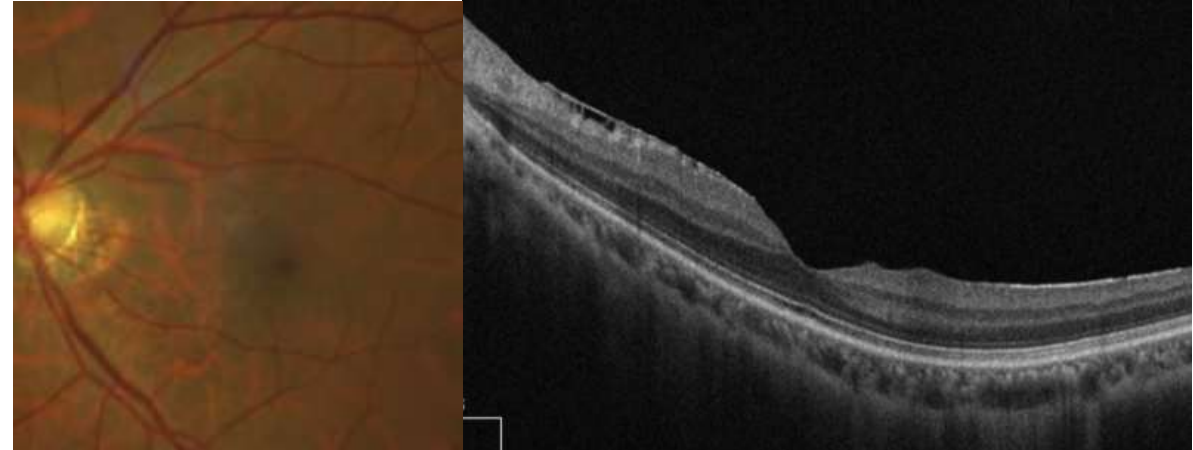
TABLE 1 Aetiology of epiretinal membranes

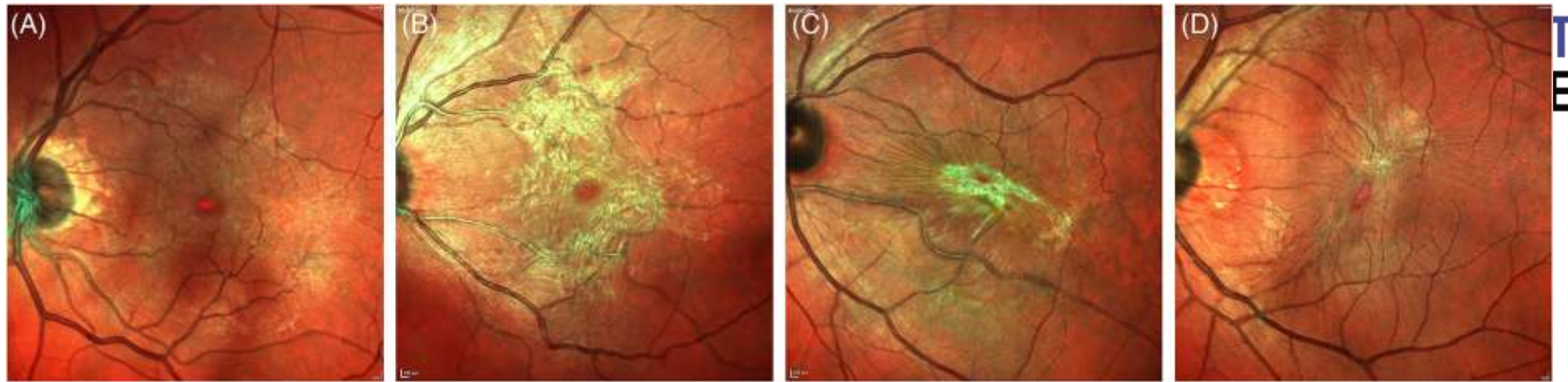
1. Idiopathic
• No pathology
• Posterior vitreous detachment only ^a
2. Secondary
• Iatrogenic
◦ Cataract surgery
◦ Vitrectomy surgery
◦ Retinopexy (laser or cryotherapy)
• Retinal vascular disease
◦ Diabetic retinopathy
◦ Retinal vascular occlusive disease
◦ Coat's disease
◦ Retinal arteriolar macroaneurysm
◦ Radiation retinopathy
◦ Sickle-cell retinopathy
• Uveitis
• Retinal tears and/or detachment
• Associated with other vitreomacular traction disorders
◦ Macular hole
◦ Vitreomacular traction syndrome
• Pathological myopia
• Trauma
• Intraocular tumours
◦ Retinal ("capillary") haemangioblastoma
◦ Vasoproliferative tumour
◦ Choroidal melanoma
◦ Combined hamartoma of the retina and retinal pigment epithelium
◦ Retinal astrocytic hamartoma
• Age-related macular degeneration
• Retinal dystrophies
◦ Retinitis pigmentosa
• Neurofibromatosis Type 2

^aConsidered by some as "primary" rather than "idiopathic."²⁰

Diagnosis of ERM

- Typically incidental and seen as a glistening fundus reflex
- Hyper-reflective line anterior to the inner retinal surface on OCT
- More advanced cases with progression feature:
 - Inner retinal distortion
 - Straightening or increased tortuosity of the retinal vessels
 - Superficial radial folds



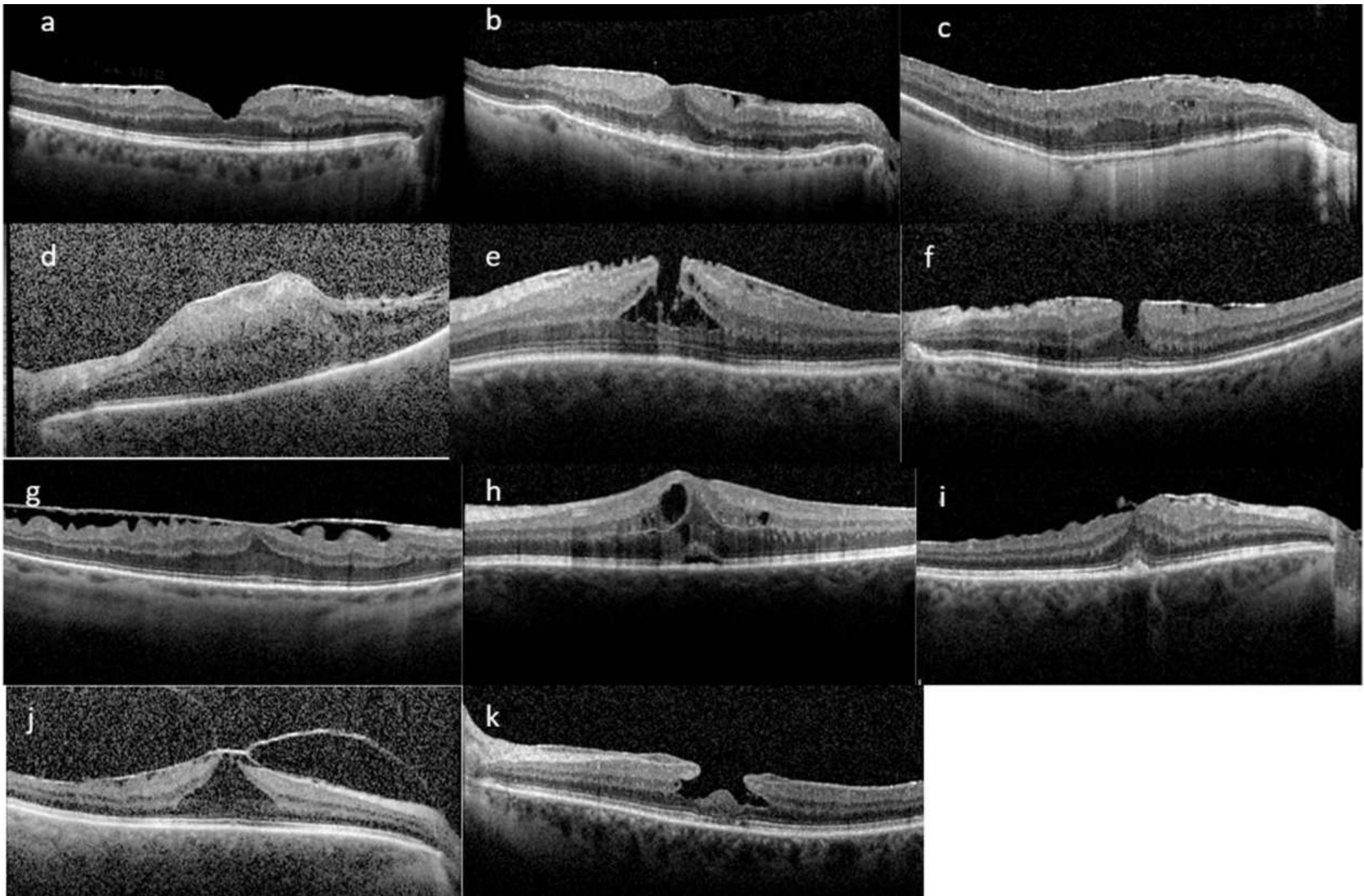


TE

Grade	0	1	2	N/A
Name	Cellophane maculopathy	Crinkled cellophane maculopathy	Macular pucker	Pseudohole
Description	Early, translucent form of ERM without distortion of the inner retina	Intermediate, translucent form of ERM with distortion of the inner retina	Late, opaque form of ERM with distortion of the inner retina	False appearance of a full thickness macular hole caused by an ERM
Synonyms	<ul style="list-style-type: none"> Cellophane macular reflex 	<ul style="list-style-type: none"> Primary retinal fold Surface wrinkling maculopathy/retinopathy ILM shrinkage/contraction 	<ul style="list-style-type: none"> Epiretinal puckering/gliosis Pre-macular/pre-retinal fibrosis 	

Workup

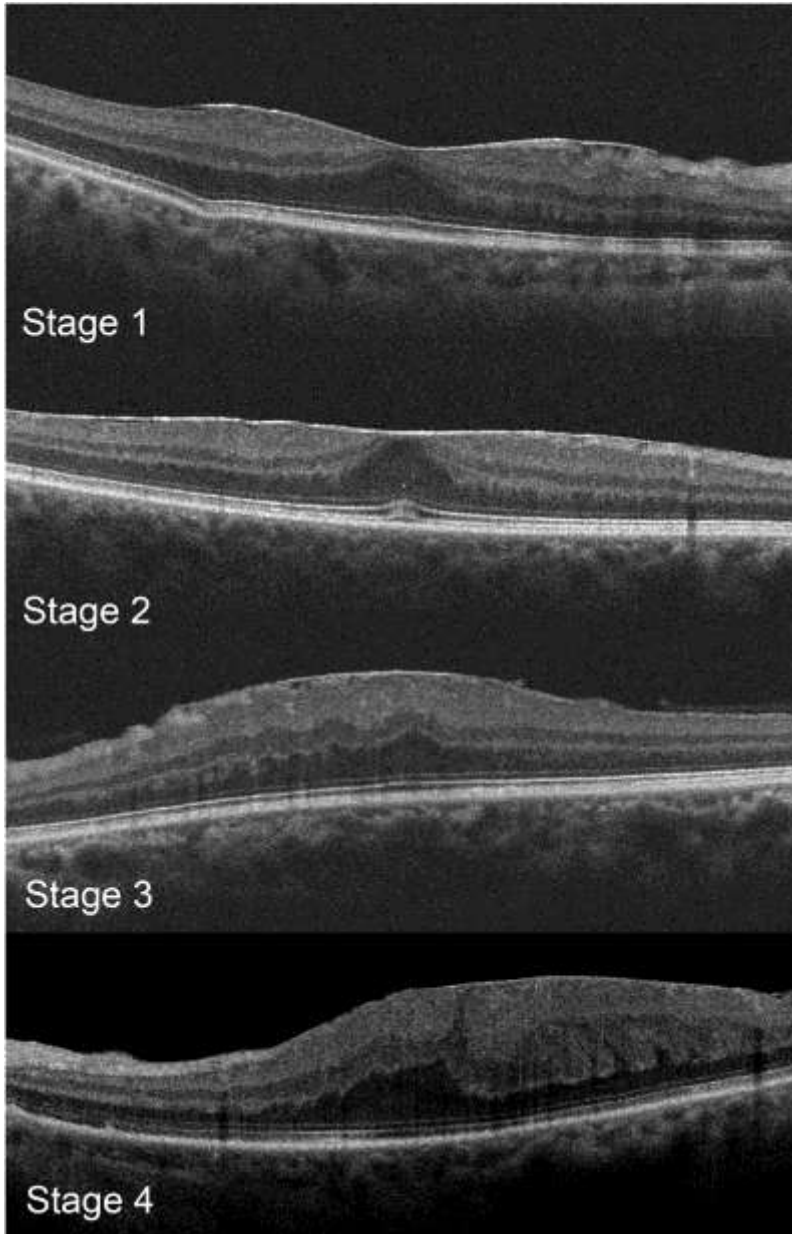
- iERM is a diagnosis of exclusion, important to dilate!
 - Rule out differential diagnoses and associated conditions
 - Check for PVD
- “OCT has become the single most useful ancillary test in the diagnosis of ERM and is more sensitive than clinical examination alone.”
 - Qualitative and quantitative analysis
 - Correlation with visual prognosis


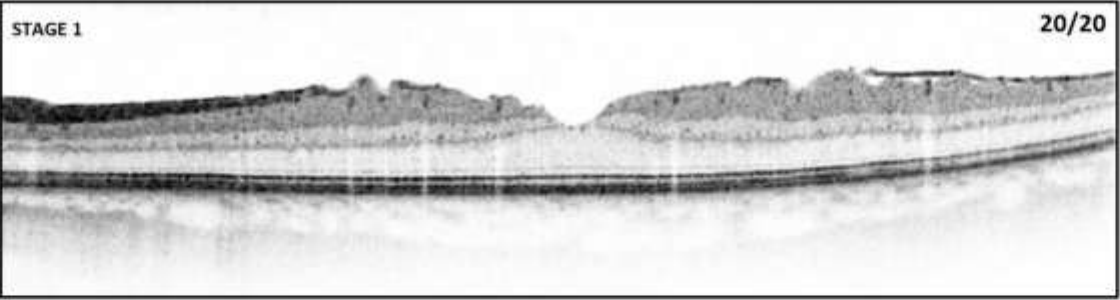

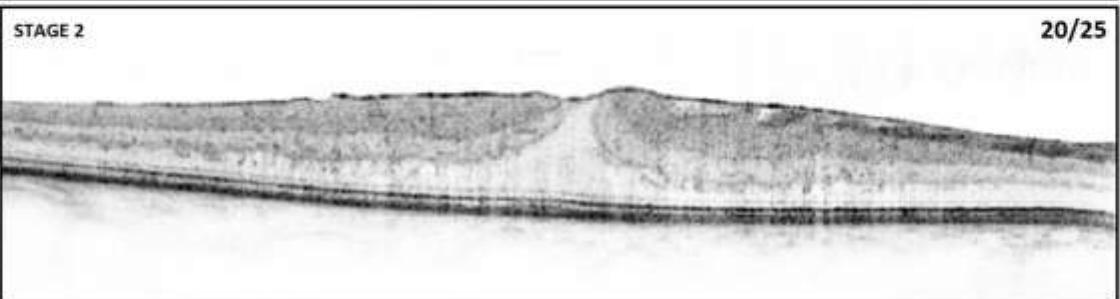
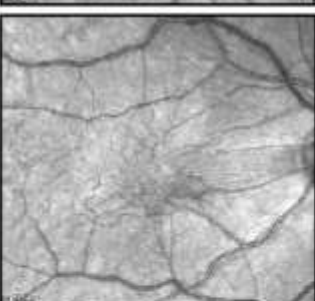
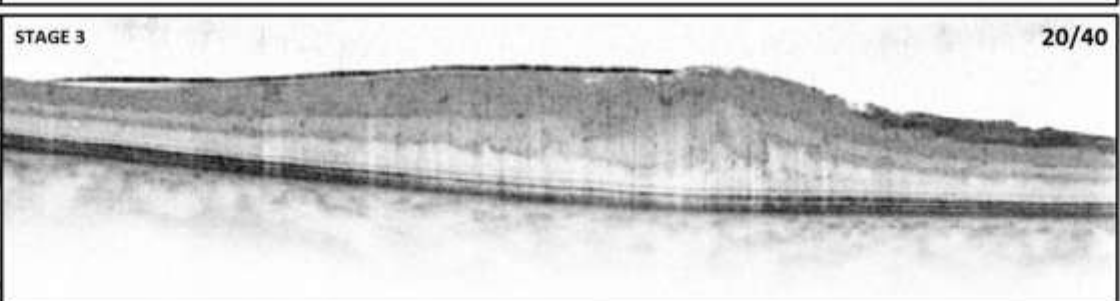
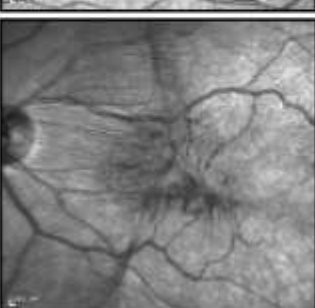
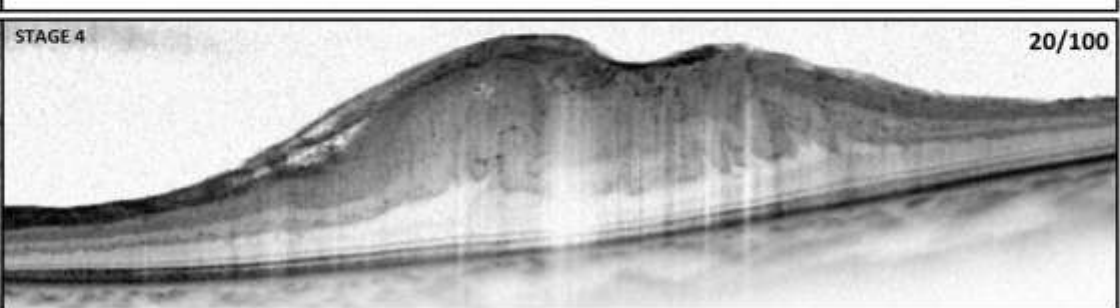


Chua PY, Sandinha MT, Steel DH. Idiopathic epiretinal membrane: progression and timing of surgery. Eye (Lond). 2022 Mar;36(3):495-503

Staging and classification scheme

- Typically describe retinal morphology using funduscopy and/or OCT, aetiology, location against retinal function
- Govetto et al. Four stage ERM classification system
 - Absence of foveal pit
 - Ectopic inner foveal layers
 - Disorganisation of the retinal layers
- Higher ERM stage correlated with poorer VA, increased central foveal thickness, CMO, EZ disruption, reduced FAZ size



	<p>STAGE 1 20/20</p> 	<p>STAGE 1</p> <ol style="list-style-type: none"> 1. Presence of the foveal pit. 2. Well-defined retinal layers.
	<p>STAGE 2 20/25</p> 	<p>STAGE 2</p> <ol style="list-style-type: none"> 1. Absence of the foveal pit. 2. Well-defined retinal layers.
	<p>STAGE 3 20/40</p> 	<p>STAGE 3</p> <ol style="list-style-type: none"> 1. Absence of the foveal pit. 2. Well-defined retinal layers. 3. Presence of ectopic inner foveal layers.
	<p>STAGE 4 20/100</p> 	<p>STAGE 4</p> <ol style="list-style-type: none"> 1. Absence of the foveal pit. 2. Disrupted retinal layers. 3. Presence of ectopic inner foveal layers.

Management

- ERM is a chronic, slowly progressive disease
- Most patients do not require intervention
- Monitor for progressive:
 - Visual decline – visual acuity and symptoms
 - Retinal thickening and other structural changes
- Over 5-years in the BMES:
 - 29% progress
 - 39% stable
 - 26% regress

Key question: Would this patient benefit from surgery?

Management

- Historical criteria for surgery:
 - VA \leq 6/12 or 6/18 or
 - Sx affecting activities of daily living
- However, there is a well-known mismatch between OCT appearance and visual function
- Visual outcomes following surgery are related to preoperative vision so early surgery may achieve better outcomes



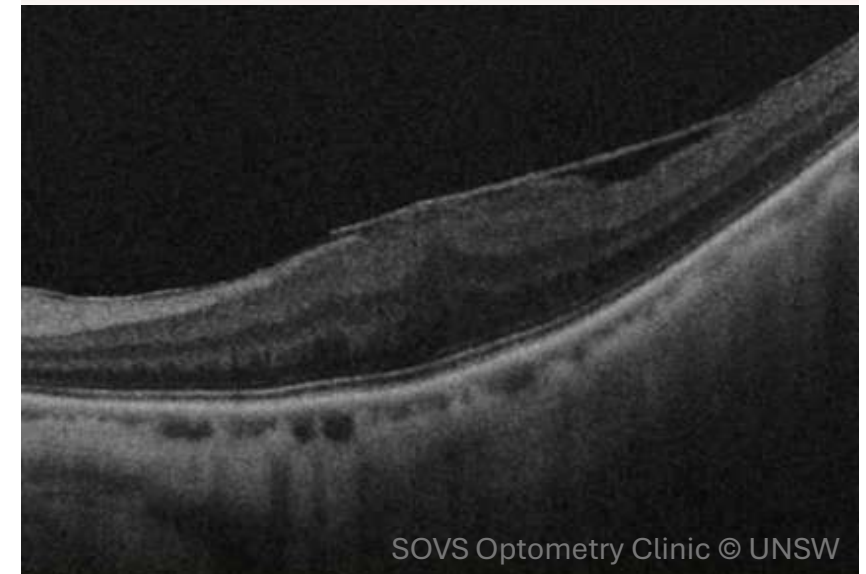
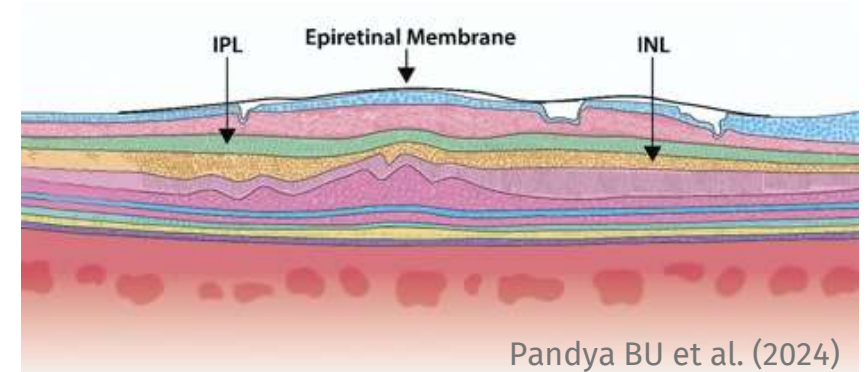
What type of biomarker would be most useful for determining whether patients with epiretinal membrane might benefit from surgery?

Predictive biomarkers in ERM

- All the following are correlated with poor post-operative VA/metamorphopsia
- Presence and thickness of ectopic inner foveal layers
- Central bouquet:
 - Cotton ball sign
 - Foveal detachment
 - Acquired vitelliform lesions
- Cystoid macular oedema
- Ellipsoid and cone RPE interdigitation zone defects
- Thicker central foveal thickness, especially INL, GCIPL layers

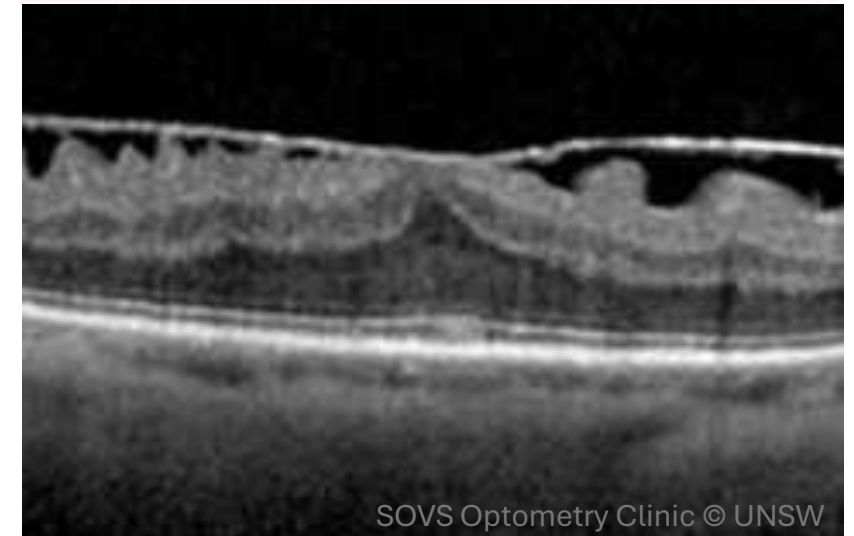
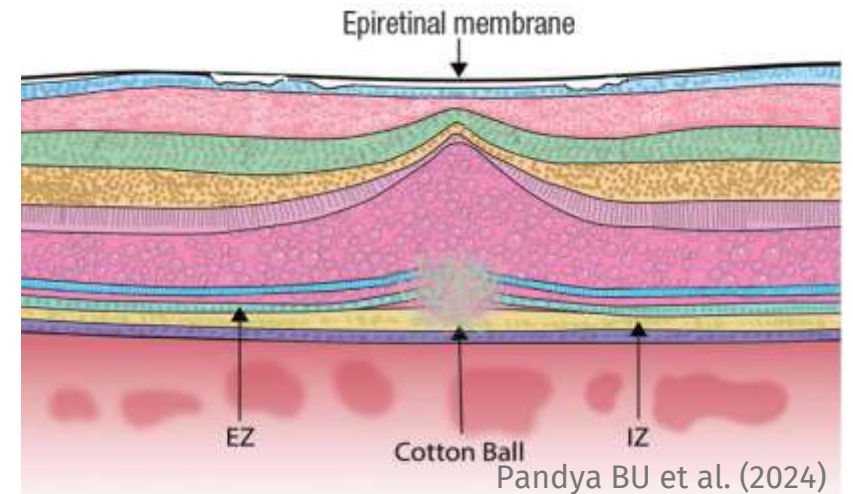
Ectopic inner foveal layers

- The presence of a continuous hypo- or hyper-reflective band extending from INL and IPL across the foveal region
- Visible in all OCT scans centred in the fovea
- Persisted (though significantly decreased in thickness) in 91% of cases after surgery
- Postoperative VA is lower in cases with EIFL vs without EIFL at baseline
- 92% of iERM patients achieved a VA of 6/12 or better after surgery, if they did not have EIFL preoperatively



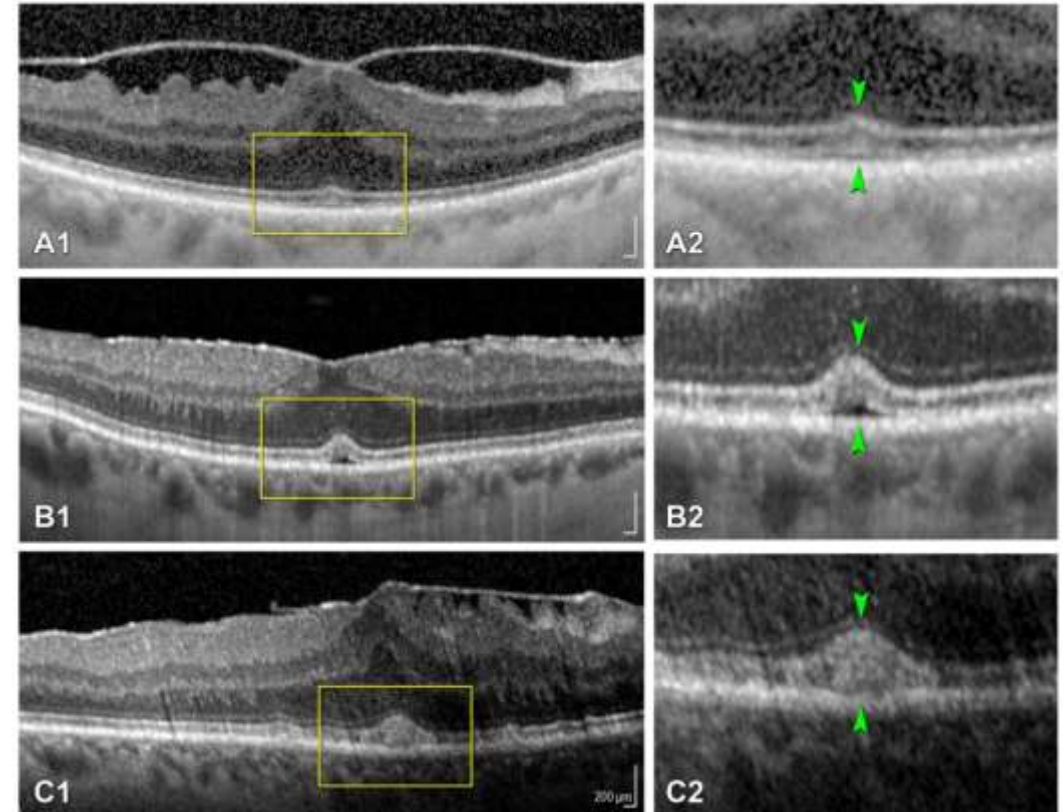
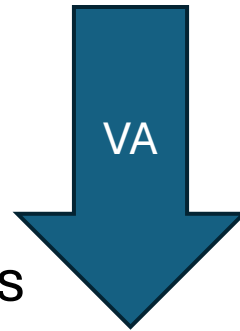
Cotton ball sign

- A round or diffuse highly reflective region typically observed between the EZ and RPE at the centre of the fovea
- Observed in 30 of 47 cases of iERM
- Associated with increased CFT in ERM
- Caused by centripetal traction that displaces the central cones in the fovea with loss of the normal photoreceptor alignment
- May be a predictor of traction chronicity, visual impairment and ERM severity
- Disappeared in half of the cases with surgery or spontaneous resolution



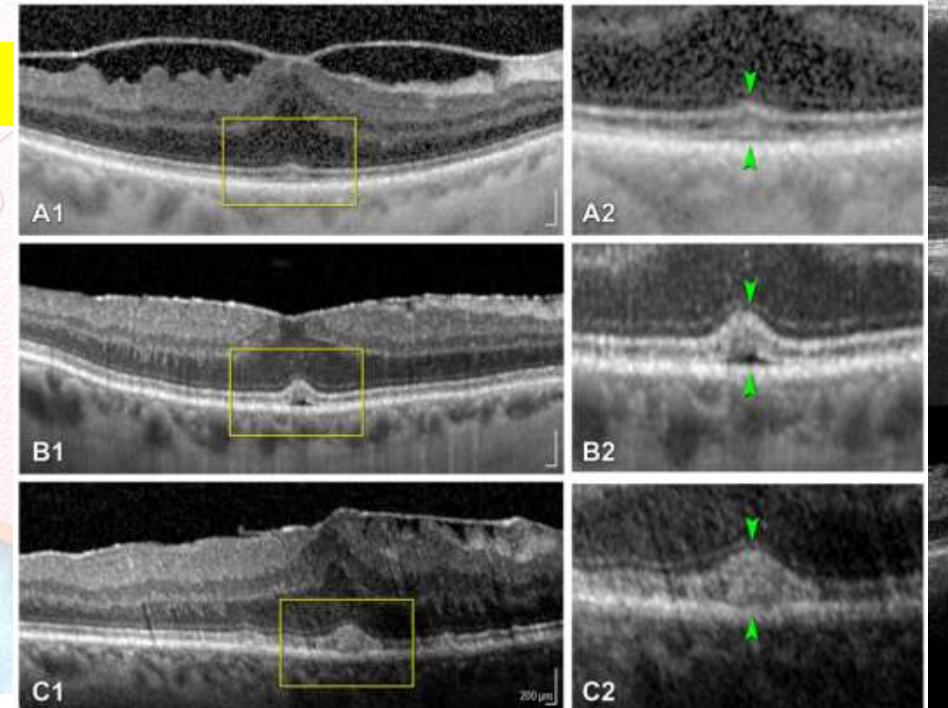
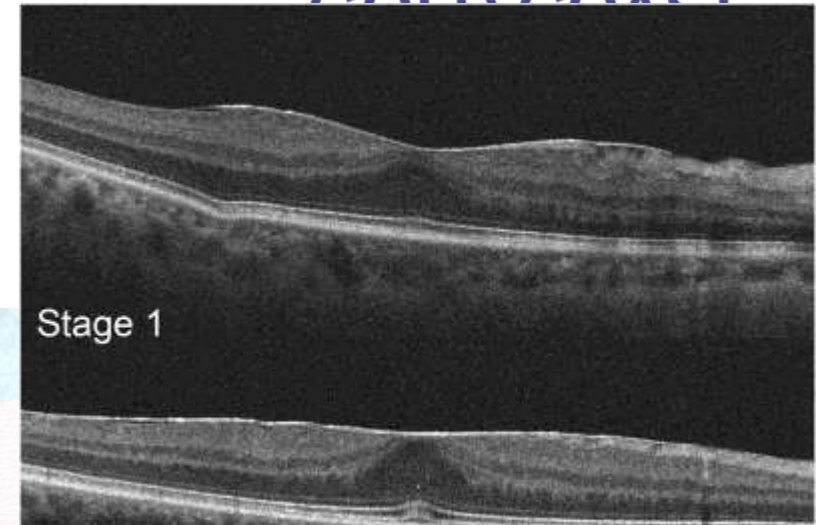
Central bouquet

- The central 100 μ m diameter zone is most susceptible to tractional damage and manifests one of three appearances in ERM:
 - Cotton ball sign
 - Foveolar detachment
 - Acquired vitelliform lesions
- Less likely to be affected in eyes with EIFL



Clinical pearl

- The optimal timeframe for surgery
 - VA \leq 6/12 or 6/18 or
 - Sx affecting activities of daily living or
 - Before the development of EIFL
- There may be a reversibility component to the damage inflicted by ERM, with recovery less likely in eyes with EIFL (ERM stages 3 and 4).



Key points for case study 3: Do you see what I see?

- Predictive biomarkers in ERM, especially EIFL, have been correlated with poor post-operative visual outcomes
- The optimal timeframe for ERM surgery could be before the development of EIFL

Key messages

- Diagnostic, prognostic and predictive biomarkers enable early detection, timely intervention and better patient outcomes
- In cases of suspected active pachychoroid spectrum disease, assess the underlying RPE and choroid
- Integrity of the outer retinal bands in AMD carry a larger risk of progression than large drusen
- The optimal timeframe for ERM surgery could be before the development of EIFL

Acknowledgements

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